

THE CHEMICAL CONTROL OF RESPIRATION IN CHRONIC

RESPIRATORY FAILURE

by

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of Edinburgh in the Faculty of Medicine.



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Last in this list, but by no means least in the debt due, are the subjects of these experiments. The normal subjects included colleagues

## PREFACE

in the University of Edinburgh, and I am fully conscious of the demands of these experiments. The bronchitic patients include many who have become almost personal friends over the years. To them all, who presumably will never read this thesis, I can only say thank you. The results may not particularly have helped them, but will, perchance, lead in some small way to an improved understanding of their disease, which may help others in the future. work.

Science has a multiplicity of definitions but the conventional Concise Oxford Dictionary one of "systematic and formulated knowledge" will suffice as a start. Karl Pearson, in his book "The Grammar of Science" extends his definition to embrace the scientific method. He states "the classification of facts, the recognition of their sequence and relative significance is the function of science". He deprecates the idea that science is merely a compendium of useful knowledge, and elevates the scientific frame of mind (by which he means the forming of judgments based upon facts, unbiassed by personal feeling) as being sufficiently justified in itself. This seems to me to be an essentially moral argument, for the practice of logical thinking, which is my interpretation of Pearson's "scientific frame of mind", appears to invoke no necessity for justification by results. This would not imply that all such results of logical thought are necessarily good. In a moral sense, but I would



## P R E F A C E

As with most prefaces, this is written after the main work, but it is still intended to be read first. It should serve two purposes, which I hope can be combined without conflict, the first to act in the manner of a Shakespearean chorus, setting the scene for the main play, and the second to allow the author to present a purely personal view of the motives underlying this work.

Science has a multiplicity of definitions but the conventional Concise Oxford Dictionary one of "systematic and formulated knowledge" will suffice as a start. Karl Pearson, in his book "The Grammar of Science" extends his definition to embrace the scientific method. He states "the classification of facts, the recognition of their sequence and relative significance is the function of science". He deprecates the idea that science is merely a compendium of useful knowledge, and elevates the scientific frame of mind (by which he means the forming of judgments based upon facts, unbiased by personal feeling) as being sufficiently justified in itself. This seems to me to be an essentially moral argument, for the practice of logical thinking, which is my interpretation of Pearson's "scientific frame of mind", appears to invoke no necessity for justification by results. This would not imply that all such results of logical thought are necessarily good, in a moral sense, but I would



submit that intellectual freedom, both to reason and to dream, is in itself morally desirable.

For most people, however, dreams and reasons must start from a present reality, and in this case the reality has been a complex problem in a disturbance of a physiological control mechanism. How does carbon dioxide fail to stimulate the breathing in patients with severe chronic bronchitis?

For the application of Pearson's definition it is apparent that the facts which are to be classified must first be ascertained. What are facts? I have no full answer, for any definition must involve truth, and real knowledge of truth eludes me. However, I can substitute for this unattainable objective of truth, by using what I believe is an honest assessment of scientific method. I may never really know anything, but if I make an honest observation, and consider to the best of my ability the possibilities of error in my observation, in my submission, I have made a contribution whose value will depend upon my abilities. My interpretation of this observation, or in Pearson's terms, my classification of my "fact" and its placement in sequence and recognition of its significance, will always be open to question, but the care with which the observation was made must indicate its proximity to infallibility. In this sense, therefore, I can merely state my complete agreement with Gray "to those physiologists whose imperishable observations provoke my perishable interpretations".

It would follow, therefore, that in my view the accuracy of the observation or the "fact", is of paramount importance. Nonetheless, observations without thought for their use, or interpretation, are unlikely to provoke a spirit of enquiry to seek new observations. A science which seeks to establish facts alone would, in my view, be sterile.

In the present study the difficulties of the problem impose their own discipline. To investigate a control system, it is desirable to study the responses of the system to known variations in a stimulus. To know about something properly, there is no substitute for measurement, to paraphrase Lord Kelvin. In this problem, therefore, measurements of both response and stimulus, and then attempts to relate these in some mathematical form are made. However, the basic problem lies in the possibility of error in these primary physical measurements of both stimulus and response. Furthermore, the accuracy with which we can measure these values, at least in the case of the stimulus, is of the same order as that which provokes a response in the stimulated system.

The manner in which I have attempted to face these problems will be shown in the following pages. I am conscious of many defects in the methods I have used, and my conclusions are drawn with a full knowledge that they are only justifiable in so far as they take account of their foundations in these possibly perishable observations.

#### NOTE OF PREVIOUS PUBLICATIONS:

Some results of this study have been previously published as:-

- 1) "The changes in the rate of human inspiratory work produced by alterations in arterial blood gas tensions and pH"

Flenley, D.C. (1964)

Quart. J. exp. Physiol., 59: 466 - 473.

This paper describes the development of methods of measurement of inspiratory work, and the results in normal subjects.

- 2) "The accuracy of blood gas electrodes"

Flenley, D.C., Millar, J.M. and Rees, H.A. (1967)

Brit. med. J. To be published.

This paper describes the calibration of the blood gas electrodes described in this thesis.

- 3) A paper entitled:

"The ventilatory response to oxygen and carbon dioxide in chronic respiratory failure"

Flenley, D.C. and Millar, J.S. (1967)

has been submitted to Clinical Science for publication.

This paper describes the results in terms of ventilatory response to carbon dioxide and oxygen mixtures in normal subjects and bronchitic patients in the main experiments of the present thesis.

4) Papers with similar titles and similar content have been read to the Medical Research Society by D. C. Flenley in December, 1965, and to the Scottish Society for Experimental Medicine by J. S. Millar in January, 1966.

## CHAPTER 1

### THE CHEMICAL CONTROL OF VENTILATION

## CHAPTER I

### THE CHEMICAL CONTROL OF VENTILATION

#### 1. The Present Position:

The modern view of the chemical control of ventilation in man may be stated as follows. Carbon dioxide stimulates breathing by a direct action of the medullary surface chemoreceptors, which are probably situated on the lateral border of the medulla, where they are sensitive to the acidity of the cerebrospinal fluid bathing these receptors. Carbon dioxide also stimulates breathing by a reflex action of the chemoreceptors of the carotid and aortic bodies, which are sensitive to the change of the acidity of the arterial blood which it produces, but in chronic states of carbon dioxide excess or depletion this effect is antagonised by active secretion or removal of bicarbonate into, or from, the cerebrospinal fluid. Oxygen deficiency stimulates respiration almost entirely by means of the carotid and aortic chemoreceptors, where the ultimate stimulation may arise from accumulation of acidic products of anaerobic metabolism within the chemoreceptor cells. Both excess acidity of the arterial blood and an increase in the partial pressure of the arterial carbon dioxide ( $P_{aCO_2}$ ) can potentiate such peripheral chemoreceptor stimulation by hypoxia. The interaction of carbon dioxide, excess acidity, and hypoxia as respiratory stimulants are well known, in a quantitative manner, but the exact mechanism of this interaction remains unknown.



## CHAPTER I

### THE CHEMICAL CONTROL OF VENTILATION

#### 1. The Present Position:

The modern view of the chemical control of ventilation in man may be stated as follows. Carbon dioxide stimulates breathing by a direct action of the medullary surface chemoreceptors, which are probably situated on the lateral border of the medulla, where they are sensitive to the acidity of the cerebrospinal fluid bathing these receptors. Carbon dioxide probably exerts its stimulation by reason of the change of the acidity of the cerebrospinal fluid which it produces, but in chronic states of carbon dioxide excess or depletion this effect is antagonised by active secretion or removal of bicarbonate into, or from, the cerebrospinal fluid. Oxygen deficiency stimulates respiration almost entirely by means of the carotid and aortic chemoreceptors, where the ultimate stimulation may arise from accumulation of acidic products of anaerobic metabolism within the chemoreceptor cells. Both excess acidity of the arterial blood and an increase in the partial pressure of the arterial carbon dioxide ( $\text{PaCO}_2$ ) can potentiate such peripheral chemoreceptor stimulation by hypoxia. The interaction of carbon dioxide, excess acidity, and hypoxia as respiratory stimulants are well known, in a quantitative manner, but the exact mechanism of this interaction remains unknown.

This modern view is the achievement of over 100 years of active research into these problems, and the history of these discoveries presents a fascinating story.

## 2. Carbon Dioxide:

In 1756, Joseph Black was awarded the degree of M.D. by the University of Glasgow for a thesis entitled "Experiments on Magnesia Alba, Quicklime, and Some Alkaline Substances". In this he described the discovery of "fixed air", obtained by heating limestone or chalk, and detected by its property of rendering limewater milky. Black proceeded to demonstrate the production of fixed air by human respiration, when in 1764 he arranged that rags soaked in limewater should be placed in the air vent of a church. As a result of the religious exertions of some 1,500 persons in the building over ten hours, he obtained a considerable quantity of crystalline lime from his rags.

Lavoisier further confirmed that "fixed air" was indeed involved in the processes of animal metabolism, wherever oxygen was consumed. The first experiments describing the effects of carbon dioxide (as "fixed air" was later recognised) were reported by Pflüger in 1868, but his conclusions of the relative inefficiency of carbon dioxide, as opposed to oxygen lack, as a ventilatory stimulant, doubtless arose from his use of 30% carbon dioxide which most authorities would today regard as a narcotic.

However, a chauvinistic pride is gratified by the realisation that Marshall Hall, in 1850, had in fact first suggested that the blood carbon

dioxide was "the real exciting cause of inspiration", although he apparently considered that the gas acted by stimulating the pneumogastric (or vagus) nerves. The first quantitative results on the relationship between the carbon dioxide concentration in exhaled air and the ventilation in man were reported by Miescher-Rusch in 1885. He concluded that the resting human ventilation was primarily regulated by carbon dioxide concentrations.

In 1905, J. S. Haldane published his first contribution to this field (Haldane and Priestley, 1905). By means of their alveolar gas sampling tube, which produced a sample of gas from the very end of a deep expiration, these authors demonstrated that the alveolar  $\text{PCO}_2$  remained remarkably constant at 40 mm.Hg. at Oxford, with a barometric pressure of 755 mm.Hg, on the summit of Ben Nevis, despite soaking with rain and a barometric pressure of 646.5 mm.Hg, at the bottom of the Dolcoath Mine in Cornwall, with a barometric pressure of 832 mm.Hg, and finally in the pressure chamber in the Brompton Hospital at a barometric pressure of 1260 mm.Hg.

During these various conditions the alveolar  $\text{PO}_2$  showed very considerable variation from 62 to 447 mm.Hg. Again, in this famous paper, these authors went on to demonstrate that a rise of  $\text{PCO}_2$  of 0.2% of an atmosphere doubled the ventilation of the lung alveoli. The constancy of the alveolar  $\text{PCO}_2$  was confirmed by Fitzgerald and Haldane (1905) who gave extended results of alveolar  $\text{PCO}_2$  for men, women, girls and boys, at Oxford.

Thus in 1905 it appeared that carbon dioxide was of most importance in the regulation of human ventilation, and the body regulated ventilation so

as to maintain a constant alveolar  $\text{PCO}_2$ .

### 3. Hydrogen Ion Concentration:

Walter (1877) was the first to describe the ventilatory stimulation which resulted from administering large doses of dilute hydrochloric acid to rabbits, although the effect was much less marked in the dog. The relationships between the carriage of carbon dioxide and the acidity of the blood were the subject of the early work of Laurence Henderson, and his classic paper "The theory of neutrality regulation in the animal organism" (1908) was the first application of the Law of Mass Action to the dissociation of carbonic acid in living tissues. His equation and the subsequent transposition into the logarithmic form by Hasselbach (1916) to form the well known Henderson-Hasselbach equation, describe the quantitative relationship between acidity and  $\text{PCO}_2$ , in blood, or in any other fluid, if the appropriate values of bicarbonate concentration, carbon dioxide solubility, and dissociation constant of  $\text{H}_2\text{CO}_3$  for that fluid are known. Thus the scene was set for the play. Does the  $\text{PCO}_2$  or the Hydrogen Ion Concentration, of blood, or of the respiratory centre, or of brain tissue fluid, or of chemoreceptor cell fluid, determine the regulation of ventilation?

In 1911, Hans Winterstein propounded the first idea that was to become his "Reaction Theory" of the regulation of ventilation, which was based on the proposal that the acidity of the blood was the principal determinant of ventilation, and the  $\text{PCO}_2$  merely a reflection of the inevitable physico-chemical consequences of the Henderson (1908) equation. This theory



received great support from experiments of Hasselbalch (1916), which demonstrated a fall in the alveolar  $\text{PCO}_2$  of 4.4 mm.Hg during a period on an acid producing diet, in man, whereas the blood pH remained relatively constant. Similar results supporting the Reaction Theory arose from Hasselbalch and Lindhard (1915) who showed that the blood pH fell during the hyperventilation induced by hypoxia of simulated altitude. These results convinced Haldane, who accepted this Reaction Theory (Haldane and Priestley, 1934). Campbell, Douglas, Haldane and Hobson (1913) showed that the ventilatory response to inhaled carbon dioxide could be studied quantitatively in man by means of an approximately steady state technique. As well as noting the individual variation in results that has bedeviled all subsequent work in this field, these authors also showed that "it appears that a rise or fall of 0.22% or 1.5 mm.Hg in the alveolar carbon dioxide is sufficient to increase or diminish by 100% the resting alveolar ventilation". They concluded, with that prophetic foresight at which Haldane's successors can only marvel, that changes of this magnitude in the alveolar carbon dioxide must reflect very small changes in the acidity of the blood, and that the sensitivity of the respiratory centre to acidity must be greater than that of any then known measuring instrument. The position today remains unchanged, as later discussion will show.

This period, however, bristled with controversy, and not only in the blood soaked mud of the Somme. The Reaction Theory, which was so named by Winterstein in 1921, had proposed a total explanation of respiratory control,

In addition to change of carbon dioxide, and blood pH, the reaction of these



involving the hypoxic drive to ventilation as well as responses to acidity and carbon dioxide. The idea was that anaerobic metabolism, consequent upon the hypoxia, produced acidic metabolites into the blood stream, particularly lactic acid, and that the ventilatory stimulation from hypoxia arose from this cause. The earlier results of Hasselbalch and Lindhard (1912) had supported this view. In 1920, Haggard and Y. Henderson, in a paper entitled "The Fallacy of Asphyxial Acidosis" attacked this view, pointing out that in fact the blood became more alkaline, and not more acidic, during exposure to hypoxia. This arose, as they showed, from the excess elimination of carbon dioxide in the very act of hyperventilation, for the alveolar  $\text{PCO}_2$  fell at high altitudes (Ward, 1908). The difficulties of examining a system of negative feedback control were very apparent. Which came first, an acidity from hypoxia, or an alkalinity from hyperventilation? And, if the former, why did the hyperventilation continue despite this alkalinity, if the drive to ventilation was indeed the acidity of the blood? Haldane, Kellas and Kennaway (1919) agreed with Y. Henderson's criticism of the Reaction Theory on this point. The demonstration that carbon dioxide was about 30 times more potent than fixed acid in provoking respiratory stimulation (Hooker, Wilson and Cornett, 1917) was another blow to the Reaction Theory.

In 1921, therefore, Winterstein published an adaptation of his theory. This second Reaction Theory postulated that the acidity of the cells of the respiratory centre, and not of the blood, was the determinant of ventilation. In addition to change by carbon dioxide, and fixed acid, the reaction of these

cells was also dependent upon the presence or absence of anaerobic metabolites. The ingenious nature of this theory has led to its widespread acceptance, but one cannot resist the observation that complete inability to measure the acidity of the "respiratory centre" may possibly be one reason for the continued success of this theory. Support for the theory was provided by Jacobs (1920) illustrating the effects on the intracellular pH of tadpoles, carnations, and arcabio eggs, of changing the extracellular fluid from alkaline carbon dioxide - bicarbonate mixtures to organic acids. In the first case, carbon dioxide diffused into the cell, unlike the organic acids, and changed the intracellular pH as shown by indicator dyes. Gesell (1925) elaborated this form of the Reaction Theory, and Gesell and Hertzmann (1926) showed that the pH of cerebrospinal fluid could change in an opposite direction to that of arterial blood.

#### 4. The Cerebrospinal Fluid:

The role of carbon dioxide in stimulating respiration remained therefore as a direct action on the "respiratory centre", perhaps acting through changes in intracellular pH, for about 20 years or more. The only advance in this time, in this field, was in the discovery of the carotid and aortic chemoreceptors, and the part they played in mediating respiratory responses to hypoxia (vide infra). However, in 1950, Leusen first reported that the respiratory activity of the anaesthetised animal could be influenced by changing the acid base balance of the fluid of the cerebral ventricular system. These studies indicated that respiratory activity was increased

by raising  $\text{PCO}_2$  and  $(\text{H}^+)$  concentration within the cerebral ventricular system, whereas a fall in  $\text{PCO}_2$  and  $(\text{H}^+)$  concentration had a converse effect. These experiments were extended and confirmed in 1954 (Leusen, 1954 a) and b). At that time the site of the chemosensitive areas within the cerebral ventricular system was unknown, but Loesche, Koepchen and Gertz (1958) suggested that this lay in the lateral recesses of the fourth ventricle. The experiments of Mitchell, Loeschke, Masson and Severinghaus (1963) have led to the localisation of the chemosensitive areas on the ventrolateral surface of the medulla, at least in the cat and the dog.

The manner in which these areas are stimulated has led to much work. In 1920, Collip and Backus showed that the cerebrospinal fluid pH was regulated more constantly than that of blood. Cerebrospinal fluid, however, is a weak solution of bicarbonate lacking the amphoteric arms of haemoglobin or plasma proteins to absorb excess hydrogen ions. Thus, if indeed cerebrospinal fluid in vivo is better buffered than blood, then transport of bicarbonate ions into the cerebrospinal fluid must be occurring against a concentration gradient. The most direct evidence that such transport does in fact occur was provided by Severinghaus, Mitchell, Richardson and Singer (1963). They showed that in man, during acclimatisation to high altitude, the cerebrospinal fluid pH remained within normal limits (pH 7.31 - 7.33) despite a dramatic rise in blood pH following on the hyper-ventilation occurring at high altitude. The bicarbonate concentration of the cerebrospinal fluid must have fallen during this period of acclimatisation, and this was found to have occurred, the plasma  $\text{HCO}_3^-$  falling about



2 mEq/litre, and cerebrospinal fluid  $\text{HCO}_3^-$  by 4 to 5 mEq/litre. The authors concluded that cerebrospinal fluid bicarbonate concentration was actively regulated during their experiments.

This result led the same group to examine data on cerebrospinal fluid pH regulation in other disturbances of acid base balance. Gathering data from the literature (Mitchell, Carman, Severinghaus, Richardson, Singer and Schnider, 1965) they proposed that cerebrospinal fluid pH was regulated in the normal limits in all disorders of blood acid base balance; respiratory alkalosis (altitude acclimatisation), metabolic alkalosis (Bradley and Semple, 1962); metabolic acidosis (Bradley and Semple, 1962; Cowie, Lambie and Robson, 1962; Schwab, 1962; Pauli Vorbürger and Reubi, 1962); and respiratory acidosis (Schwab, 1962; Buhlmann, Schietlin and Rossier, 1963; Merwath, Sieker and Manfredi, 1961). This important hypothesis was not, on close examination, supported by all the evidence quoted, particularly in severe states of renal acidosis (Cowie, Lambie and Robson, 1962) or in severe respiratory failure. This latter point is, of course, of great interest from the point of view of this present work. Further results supporting the finding of increased acidity of the cerebrospinal fluid in severe respiratory acidosis were presented by Huang and Lyons (1966) who claimed to show that the lumbar cerebrospinal fluid was not kept at normal pH levels as the arterial  $\text{PCO}_2$  rose above 70 mm.Hg in states of chronic respiratory failure.

This whole concept of the constancy of the cerebrospinal fluid pH has recently been challenged by the elegant studies of Pappenheimer and his

colleagues. These workers have trained goats of human size to remain standing quietly, breathing through respiratory valves, whilst ventricular and cisternal cerebrospinal fluid and carotid blood is sampled through permanently implanted cannulae. Furthermore, these animals can be examined during inhalation of carbon dioxide mixtures and in states of induced metabolic alkalosis and acidosis. From these unanaesthetised animals, therefore, it was possible to obtain data on the relationships between cerebrospinal fluid and ventilation during all varieties of acid base disturbance (Pappenheimer, Fencel, Heise and Held, 1965; Fencel, Miller and Pappenheimer, 1966). The authors conclude that the pH of cisternal cerebrospinal fluid varies continuously with the arterial bicarbonate variation in these conditions, and that the logarithm of the alveolar ventilation is related linearly to the hydrogen ion concentration of the cisternal cerebrospinal fluid in the steady state. In this result, therefore, the authors are in contradiction to the postulates of Mitchell and Severinghaus and their colleagues.

If one accepts the conclusion of Pappenheimer and his co-workers, combined with the anatomical observations of Mitchell and his colleagues, the reasoning behind the statement of the present position in chemical control of respiration, as stated at the start of this chapter, may now be clear. It is still not apparent, however, as to how the central respiratory chemoreceptor, dependent upon the acidity of the thin film of overlying fluid, will work. A little pure speculation may perhaps be allowed.

It will be recalled that Gesell (1925) utilised Jacobs (1920) demonstration of the independence of intracellular cerebrospinal fluid from the pH of the



extracellular fluid, to support Winterstein's (1921) Reaction Theory. A modern development of these views are provided by some recent experiments of Adler, Roy and Relman -(1965 a and b). Using the DMO method of determining the intracellular pH (Waddell and Butler, 1959), of the isolated rat diaphragm, they showed that this acidity depended both on the  $\text{PCO}_2$  and the bicarbonate concentration of the external fluid, but that the external  $\text{PCO}_2$  was of more importance in determining the intracellular pH than the external  $\text{HCO}_3^-$ . Furthermore, their results show that the intracellular pH is relatively constant, despite variation of external  $\text{PCO}_2$  between 45 and 65 mm.Hg, if the external bicarbonate is approximately in the normal range. If the bicarbonate is low (metabolic acidosis) or unduly high (metabolic alkalosis), the intracellular pH varied continuously with external  $\text{PCO}_2$ . Although it be a far cry from this isolated rat diaphragm to the human respiratory centre, it is not so far as from the tadpoles and arcabio eggs studied by Jacobs (1920). If these results on the rat diaphragm do, in fact, predict the manner in which the human chemoreceptor cells work, then indeed the ratio of intracellular to extracellular hydrogen ion concentration (which, by the Donnan Equilibrium, is proportional to the ratio of intracellular to extracellular potassium concentration, which in turn determines the resting membrane potential of the cell) will be dependent upon both  $\text{PCO}_2$  and  $\text{HCO}_3^-$  of the extracellular fluid. When this is the cerebrospinal fluid, which is itself not the same as the arterial blood in values of  $\text{PCO}_2$  and  $\text{HCO}_3^-$ , as we have discussed, then the possibilities for variation between blood  $\text{PCO}_2$ , ( $\text{H}^+$ ), and  $\text{HCO}_3^-$  concentration and the regulation of ventilation,

are indeed wide. The temptation to extend this speculation to calculation of probable ratios of ( $H^+$ ) ion concentration within and without the cell for various combinations of cerebrospinal fluid (and blood)  $HCO_3^-$  and  $PCO_2$  levels, is not rewarding, however, due to the sparse nature of the data available from Adler, Ray and Relman's work. One feels, however, that this question of Winterstein's masterly retreat into the cell will only ever be followed experimentally by an approach such as this.

#### 5. Oxygen Deficiency:

On 1st August, 1774, Joseph Priestley used his new 12" burning glass to focus the sun's rays onto mercuric oxide, and collected the gas evolved. This gas, which he named "dephlogisticated air", in pursuit of the phlogiston theory of combustion, in which he was an ardent believer, was later found by Lavoisier to be consumed in human respiration. It had long been known that mountain sickness, presenting with weakness, breathlessness, palpitations and headaches, could be cured by descent to lower altitudes. Between 1870 and 1885, Paul Bert carried out a brilliant series of experiments that demonstrated that the physiological effects of high altitudes arose from the diminution in the partial pressure of oxygen ( $PO_2$ ) in the inspired gas (Bert, 1878). From his experiments on cats, guinea pigs, sparrows and himself in a chamber at a simulated altitude of 28,000 feet, he concluded "Oxygen tension is everything, barometric pressure itself does nothing or almost nothing". Somewhat earlier, Pflügers work (1868) on the control of ventilation in dogs had included oxygen deficiency as well as the experiments

with 30% carbon dioxide noted earlier. He had considered oxygen lack as the more powerful stimulant, but, of course, 30% carbon dioxide is a narcotic level of this gas. Rosenthal (1862) considered that the oxygen content of the blood controlled ventilation, with little effect at all from carbon dioxide, but Hoppe-Seyler in 1879 showed that the arterial blood was almost fully saturated with oxygen when breathing air, and furthermore that changing from oxygen to air in a spirometer scarcely altered the ventilation.

The true importance of the  $\text{PCO}_2$  and not oxygen tension of the alveolar gas (which in normal man was almost equal to the arterial blood in  $\text{PO}_2$  and  $\text{PCO}_2$ ), in regulating ventilation was, of course, revealed by the work of Haldane and Priestley (1905). In his own experiments on hypoxia (Boycott and Haldane, 1908), using "the large steel chamber recently presented to the Lister Institute by Dr. Ludwig Mond", Haldane showed that the alveolar  $\text{PCO}_2$  only began to fall as the inspired  $\text{PO}_2$  fell below 116 mm.Hg, when the alveolar  $\text{PO}_2$  was about 60 mm.Hg. They also concluded "want of oxygen is at best a very feeble direct stimulus to respiration".

It will be recalled that Winterstein's first form of the Reaction Theory (1911) proposed that hypoxia acted as a ventilatory stimulant by producing an acidosis in the blood. However, Haggard and Henderson (1920) challenged this suggestion and Haldane, Kellas and Kennaway (1919) concurred in this view. The hypoxic hyperventilation in fact produced an alkalosis due to excess hyperventilation. With the elaboration of the Reaction Theory to consider the pH within the respiratory centre as the factor regulating ventilation as important, this criticism was met. It remained accepted teaching that hypoxia



acted in this site until 1927.

In that year, Heymans and Heymans published their massive contribution, demonstrating by an elegant cross circulation technique that the carotid and aortic region of the dog contained structures sensitive both to changes in blood pressure, and to deprivation of oxygen and excess of carbon dioxide in the blood flowing through this region. "L'asphyxie et l'hypotension uniquement périphériques, excitent d'une manière reflexe, l'amplitude et la fréquence respiratoires. Ces reflexes pneumogastriques, régulateurs de l'activité du centre respiratoire, n'ont pas une origine pulmonaire directe mais bien une origine cardio-aortique . . . . En un mot, la régulation respiratoire reflexe, continue et principale, part du cœur et de l'aorte; elle est conditionnée par la pression et la composition du sang périphérique". Such are the conclusions that win the Nobel Prize.

Further studies established that this peripheral chemoreceptor activity arose from the carotid bodies (1930) and aortic bodies (1939). As Gesell emphasised in a review in 1939, this work gave "a new outlook on respiration for which physiology is deeply indebted". The intimate mechanism of the activation of this nervous activity in the chemoreceptors has largely confirmed the extended view of the Reaction Theory finally propounded by Winterstein in 1956. Niel and Joels (1963), describing experiments on single fibre preparations from the isolated cat's carotid body, conclude that the carotid glomus responds most to a combination of tissue hypoxia and hypercapnia. They suggest that the high oxygen consumption of the glomus cell is only matched by the very high blood flow to it, when both are expressed



conventionally as per unit weight of tissue. This arrangement means that the glomus operates metabolically by using only the oxygen in solution in the plasma and this is dependent on the partial pressure of oxygen in the arterial blood, and not on the oxygen content of that blood. They visualise the immediate cause of discharge of the glomus during hypoxia as due to accumulation of acidic products of anaerobic metabolism within the glomus cell exactly as proposed by the Reaction Theory. The stimulation arising from hypercapnia is thought to result from the opening of vascular shunts across the true glomus tissue, under the stimulus of a raised  $\text{PCO}_2$ , thereby depriving the true glomus cells of some blood flow. The exact mechanical arrangements of vascular resistances to function in such a fashion have not yet been actually demonstrated in the carotid body.

Recent results of bilateral removal of the carotid bodies in man have established that this chemoreceptor mechanism operates in the human. This operation has been recommended in the treatment of bronchial asthma, particularly by Nakayama (1961) who reported an improvement in 2,535 of 3,914 Japanese patients. Other workers have been less enthusiastic in their claims for therapeutic benefit. Wood, Franklin and Eastcott (1965) report on the effects of bilateral removal of carotid bodies in three patients, and conclude that their results have led them to abandon the operation. The physiological studies on two of these patients are reported in detail by Holton and Wood (1965). They showed that a preoperative response of hyperpnoea to breathing 10% oxygen was converted to a response of hypoventilation after

the operation, but the ventilatory response to 3% and 6% carbon dioxide was unimpaired postoperatively. Baroreceptor responses to passive tilt were transiently abolished postoperatively but later recovered, but both patients showed persistent hypertension as a result of the operation.

These results, therefore, strongly confirm the animal studies starting with Heymans and Heymans, and suggest that the carotid bodies are mainly, if not entirely, responsible for hypoxic ventilatory drive in man.

#### 6. The Interaction of Carbon Dioxide Excess and Oxygen Deficiency:

The previous discussion has considered the actions of carbon dioxide and acidity in stimulating respiration and the separate actions of want of oxygen, but it now remains to discuss the actions of both these stimuli acting together. This problem was first examined in a systematic manner in man by Nielsen and Smith (1951). These authors varied the inspired carbon dioxide and the inspired oxygen in such a way as to maintain a constant alveolar  $PO_2$  as the carbon dioxide rose and provoked ventilatory stimulation. They reported their results as plots of minute volume of ventilation against the alveolar  $PCO_2$  at two or three constant levels of alveolar oxygen tension. They studied two trained normal subjects, and showed that hypoxia (down to an alveolar  $PO_2$  of 37 mm.Hg) potentiated the ventilatory response to an increased level of alveolar  $PCO_2$ . In addition they showed that the relationship between alveolar  $PCO_2$  and minute volume was linear for values of  $PCO_2$  above the resting level, to a ventilation of at least 35 litres/minute.

These observations were confirmed and greatly extended by Cunningham

and Lloyd and their colleagues of the Oxford School of respiratory physiologists (Cunningham, Cormack and Gee, 1957; Lloyd, Jukes and Cunningham, 1958).

These workers suggested that the relationship between minute volume ( $\dot{V}$ ) and alveolar  $\text{PCO}_2$  and  $\text{PO}_2$  could be described by the equation:

$$\dot{V} = S (\text{PCO}_2 - B) \dots \dots \dots (1)$$

(where  $S$  is dependent upon the alveolar  $\text{PO}_2$ ) for values of alveolar  $\text{PCO}_2$  from 1 mm.Hg above the resting value, to values of  $\dot{V}$  of 80 litres/minute.

Their subjects, apart from themselves, consisted of healthy Oxford medical students. This equation was further extended to include the effects of hypoxia, so that:

$$S = D \left( 1 + \frac{A}{\text{PO}_2 - C} \right) \dots \dots \dots (2)$$

for when they plotted their experimental values of  $S$  (the slope of the observed linear relationship between alveolar  $\text{PCO}_2$  and minute volume), against the alveolar  $\text{PO}_2$ , a hyperbolic curve resulted. This emphasised that hypoxia exerted little effect on the carbon dioxide response until the alveolar  $\text{PO}_2$  fell below 50 mm.Hg. The values  $D$ ,  $A$ , and  $C$  are all constants describing the form of this hyperbola. This relationship was discussed in a further paper (Cunningham, Shaw, Lahiri and Lloyd, 1961) where the whole equation is given:

$$\dot{V} = D \left( 1 + \frac{A}{\text{PO}_2 - C} \right) (\text{PCO}_2 - B) \dots \dots \dots (3)$$

This later paper also analyses the effect of maintained metabolic acidosis by ammonium chloride in normal young men, on the carbon dioxide response. They found that acidosis resulted in a shift of the whole response to the left, that is, a reduction in  $B$ , the intercept made by the projection of the linear

STEADY STATE CO<sub>2</sub> RESPONSE

part of the carbon dioxide response curve (Figure 1), onto the  $PCO_2$  axis. The value of B was not usually affected by hypoxia, which exerted its effect principally upon S, as described above.

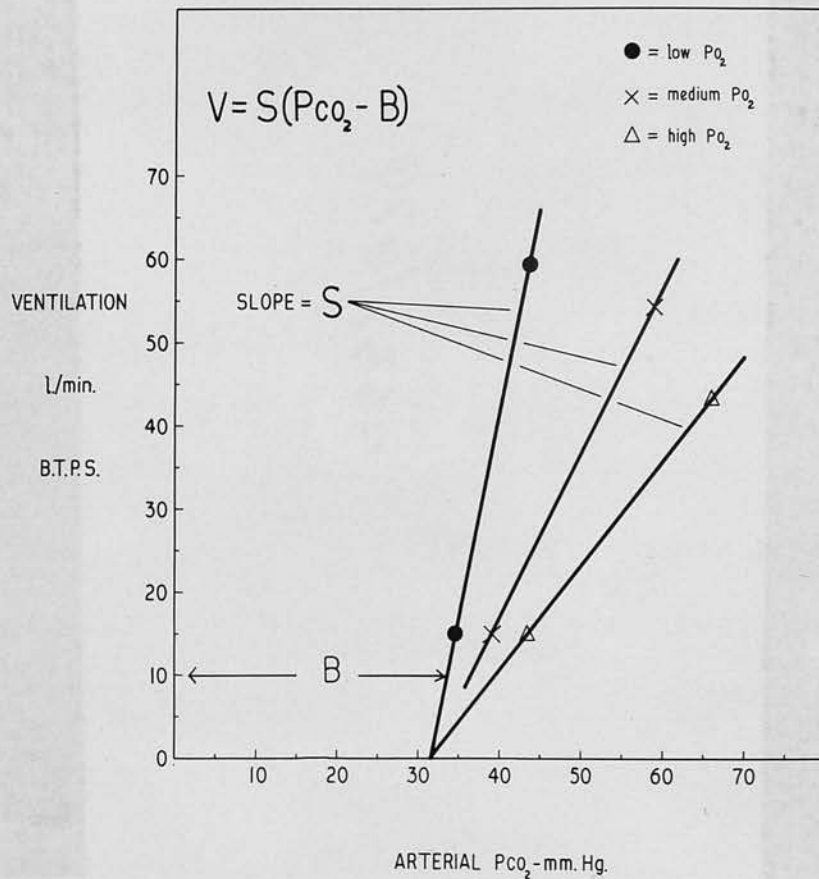
These highly important results contrasted with the "Multiple Factor Theory" advanced by Gray in 1950. His monograph was based upon a review of the literature in the field of ventilatory control. Great tribute must be paid to this work, which was undoubtedly successful in provoking much fresh interest in the field, not least in Oxford. Gray discusses the various theories of ventilatory control, from Rosenthal (1880), suggesting that hypoxia alone controlled ventilation, to Haldane and Priestley (1905) and their carbon dioxide theory, to Hasselbach (1916) and Winterstein's (1911) early form of the Reaction Theory, the later Reaction Theory (Winterstein, 1921), and then to the earlier work of Nielsen (1936) who suggested that  $PO_2$ , pH and exercise all acted as "sensitisers" to a basic stimulus dependent upon the  $PCO_2$ .

Gray rejects all these theories, as being incapable of explaining all the ventilatory responses in hypoxia, acidosis, hypercapnia and on exercise. He proposes his "Multiple Factor Theory" which basically states that the relative change in alveolar ventilation, from the resting normal level (alveolar ventilation ratio or VR) is a resultant of the additive effects of arterial hydrogen ion concentration, arterial  $PCO_2$  and arterial  $PO_2$ . Thus, from data which he gathered from the literature, he calculated the fundamental chemical stimulation equation:

$$VR_H + PCO_2 PO_2 = 0.22 H^+ + 0.262 PCO_2 - 18 + 2.118 \times 10^{-8} (104 - PO_2)^{4.9}$$



# STEADY STATE CO<sub>2</sub> RESPONSE



**Figure 1**

The relationship between ventilation and alveolar (or arterial ) PCO<sub>2</sub>, during carbon dioxide inhalation at a constant alveolar (or arterial) PO<sub>2</sub>, in the acute steady state. Modified from Nielsen and Smith (1951), Lloyd, Jukes and Cunningham (1958), and Cunningham, Shaw, Lahiri and Lloyd (1961).

It will be apparent that this form of equation differs from that used by the Oxford workers to describe their results, for they suggested that oxygen lack multiplied the carbon dioxide drive to ventilation, and did not only add to this stimulus. This conclusion of Gray's, of course, was largely based upon work in which the alveolar  $PO_2$  was not held constant as the effect of changes in the alveolar  $PCO_2$  was studied. This approach was originated by Nielsen and Smith in 1951, after the publication of Gray's monograph. However, most workers would now agree with Gray's suggestion that acidosis and hypercapnia do summate arithmetically in their ventilatory effects. In an ingenious experiment, Lambertsen, Semple, Smyth and Gelfand (1961) studied the separate effects of arterial  $H^+$  and  $PCO_2$  levels upon ventilation. They measured ventilation at two levels of arterial  $PCO_2$  and then, keeping the arterial  $PCO_2$  constant, infused sufficient bicarbonate solution intravenously to restore the arterial pH to that level originally found at the lower  $PCO_2$ , and again measured ventilation. From these experiments on five normal subjects, they concluded that the rise in  $PCO_2$  alone produced 45% of the change in minute volume and 55% of the change was the result of the change in  $H^+$  concentration in the arterial blood. Similar conclusions were shown with regard to the values of  $PCO_2$  and  $H^+$  in the internal jugular venous blood.

The particular form of interaction between arterial or alveolar  $PCO_2$  and  $PO_2$  in chronic hypoxia is of particular interest in this present study. This has been examined in acclimatisation to high altitude, where, of course,

hypoxia was greatly decreased in the last group, with mountain sickness.

a low  $\text{PCO}_2$  is combined with a low  $\text{PO}_2$ . The more clinically relevant situation of hypercapnia and hypoxia does not appear to have been studied from the point of view of interaction of  $\text{PO}_2$  and  $\text{PCO}_2$  prior to this present study. This no doubt reflects the attitudes of academic physiologists, who find it easier to obtain financial support for expeditions to high altitudes at the remote ends of the earth, than to persuade clinicians to permit studies on hypoxic patients in the teaching hospitals with which those physiologists are academically united.

Milledge (1963) applied a simplified "Oxford" type of isoxic approach to the ventilatory response to carbon dioxide during acclimatisation at 19,000 feet during the "Silver Hut" expedition to the Himalayas. Despite the difficulties of experimental physiological study in these conditions, he established that such acclimatisation is accompanied by a reduction in the values of B, in the Oxford equation (1) and also by an increase in the value of S at any given level of  $\text{PO}_2$ , and this change was almost entirely due to a two-fold increase in D, in the extended form of the Oxford equation (3). This value D is a measure of the sensitivity to carbon dioxide in the absence of hypoxia. This result was predictable, in light of the findings of Kellogg, Pace, Archibald and Vaughan (1957) who worked at a lower altitude of 12,470 feet. In a study at 14,300 feet, Bainton, Carcelan and Severinghaus (1965) found that the ventilatory response to carbon dioxide was the same in newly acclimatised visitors, permanently acclimatised residents and in residents with chronic mountain sickness. However, the ventilatory response to hypoxia was greatly decreased in the last group, with mountain sickness.

They suggest that "with long residence at high altitude, the medullary carbon dioxide chemoreceptor remains normal, while the peripheral (carotid and aortic body) chemoreceptors lose sensitivity to hypoxia, especially in chronic mountain sickness".

In summary, the interactions of  $\text{PCO}_2$ ,  $\text{H}^+$  ion and  $\text{PO}_2$  are well known in normal man, but, as we shall see later, little studied in disease. Although there is evidence of interaction at the level of the carotid chemoreceptors, the main site for such interaction would logically appear to be located in the "integrative action of the nervous system" (Sherrington).

#### CHAPTER III

### RESPIRATORY FAILURE IN CHRONIC LUNG DISEASE



## CHAPTER II

### RESPIRATORY FAILURE IN CHRONIC LUNG DISEASE

#### 1. Previous Definition

Respiratory failure is a term which has come into increasing use in clinical medicine in the last ten years. It appears to have first been used in the modern sense by Mott and Davies (1925). They refer to the effects of prolonged breathing through a resistance, as described by

## CHAPTER II

### RESPIRATORY FAILURE IN CHRONIC LUNG DISEASE

Respiratory Failure the title of his Goulstonian Lecture to the Royal College of Physicians of London (Mott, 1935). Although he does not define the condition precisely, he believed the term was "closely analogous to the familiar term cardiac failure". It is interesting that when discussing therapy of the condition, he realises that "oxygen therapy is likely to be more effective if based upon estimation of the arterial oxygen tension", and he recognised that the carbon dioxide tension of the arterial blood could also be above or below normal in respiratory failure.

The modern view has been most clearly stated by Aron (1960) as "Respiratory failure can be defined simply as that condition in which the amount of oxygen and carbon dioxide in the blood-stream is altered by an

## CHAPTER II

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#### 1. Previous Definition:

Respiratory failure is a term which has come into increasing use in clinical medicine in the last ten years. It appears to have first been used in the modern sense by Meakins and Davies (1925). They refer to the effects of prolonged breathing through a resistance, as described by Davies, Haldane and Priestley (1919), and conclude "after a certain point the respiratory centre can no longer respond normally to the effects of increased carbon dioxide and oxygen want". In 1935, Dr. Moncrieff made Respiratory Failure the title of his Goulstonian Lecture to the Royal College of Physicians of London (Moncrieff, 1935). Although he does not define the condition precisely, he believed the term was "closely analogous to the familiar term 'cardiac failure'". It is interesting that when discussing therapy of the condition, he realises that "oxygen therapy is likely to be more effective if based upon estimation of the arterial oxygen tension", and he recognised that the carbon dioxide tension of the arterial blood could also be above or below normal in respiratory failure.

The modern view has been most clearly stated by Arnott (1960) as "Respiratory failure can be defined simply as that condition in which the amount of oxygen and carbon dioxide in the blood-stream is altered by an

abnormality of the respiratory system". He goes on to recognise a "preliminary stage of respiratory insufficiency in which blood gas levels, normal at rest, become abnormal during exercise". This view is shared by Bates and Christie (1964) who write "respiratory failure may be said to be present when the tension of respiratory gases in the blood leaving the lungs is no longer within physiological limits". They note an obsolete use of term to describe failure of tissue respiration despite normal arterial blood gas tensions. Campbell (1965), with characteristic logical pugnacity, crystallises these previous definitions by giving actual values of arterial blood gas tensions in his definition. Thus "respiratory failure is present in a subject at rest breathing air at sea-level, if, because of impaired respiratory function, the arterial blood  $PO_2$  is below 60 mm.Hg or the  $PCO_2$  is above 49 mm.Hg". He recognises that these limits are somewhat above the usual normal limits (vide infra) but they appear to him to be clinically useful.

Before going on to discuss these normal values for arterial blood gas tensions, it appears important to point out that all these recent definitions carry the implication that respiratory exists when either  $PO_2$  or  $PCO_2$  levels are abnormal. The shape of the oxyhaemoglobin dissociation curve, characteristically sigmoid so that arterial saturation increases very little as arterial  $PO_2$  rises above 100 mm.Hg, differs markedly from the carbon dioxide dissociation curve of whole blood. The carbon dioxide curve is almost linear in the physiological range and much steeper than the oxygen curve. As a result hyperventilation of an area of lung which is perfused by

blood can remove an increased amount of carbon dioxide, but add very little oxygen, to the blood traversing such a pulmonary capillary. This hyperventilation of one area of lung can compensate, or overcompensate, for lack of ventilation of another perfused area, at least as far as carbon dioxide removal is concerned, but cannot fully compensate in terms of the oxygen content of the blood. This difference in the shapes of the oxygen and carbon dioxide dissociation curves, therefore, accounts for the existence of two varieties of respiratory failure. In the first the arterial  $PO_2$  is low, (by definition), but the arterial  $PCO_2$  may be normal or even low. In the second variety, however, known sometimes as "ventilatory failure", the arterial  $PO_2$  is low, and the arterial  $PCO_2$  is raised. This implies that this situation will only arise when the overall ventilation is inadequate. Although in a theoretical model carbon dioxide retention and hypoxia can result from extreme imbalance of the distribution of ventilation and perfusion in the lung, in practice "ventilatory failure" is a fair description of this combination, but, of course, ventilatory inadequacy is very commonly found in conditions where ventilation perfusion relationships are grossly disturbed. The point is really that an overall minute volume of ventilation, which may be sufficient to maintain normal blood and gas relations in a normal lung, may be insufficient to do so in a lung with a great increase in physiological dead space, resulting from ventilation and perfusion imbalance.

Clinical conditions associated with respiratory failure of the first type, that is hypoxia without carbon dioxide retention, include lobar pneumonia,



left ventricular failure, most cases of bronchial asthma in an attack, thrombo-embolic pulmonary hypertension and pulmonary fibrosis of the "alveolar capillary block" type, (particularly on exercise). Common causes of the second type of respiratory failure (with low arterial  $PO_2$  and high arterial  $PCO_2$ ), or "ventilatory failure", include chronic bronchitis and emphysema (vide infra) and, of course, central respiratory depression from drugs or anaesthetics, and in neuromuscular disorders such as bulbar poliomyelitis, infective polyneuropathy, myasthenia gravis, myopathies, and motor neurone disease. This situation can also arise in drowning and in crush injuries of the chest. The separation of these two varieties obviously depends upon measurements of the arterial  $PCO_2$ , and this separation carries important therapeutic implications, as will be seen.

## 2. Normal Blood Gas Values:

It is apparent that the definitions of respiratory failure depend upon a knowledge of the normal values for arterial  $PO_2$  and  $PCO_2$ . As with most measurements of physical quantities, particularly in biological work, the values obtained depend upon the method. The first examination of the arterial blood obtained by direct puncture appears to be that of Barcroft and Cooke (1913). As will be discussed in more detail in Chapter VI on methods employed in the present study, this field has been revolutionised in the past 10 years by the development of direct measurements using electrodes for both the  $PO_2$  and  $PCO_2$  of blood samples. It is widely accepted that these methods are not only much more convenient than those in use previously, but also more accurate when properly calibrated. The following discussion will therefore concentrate on results using these methods.

For the oxygen tension of normal arterial blood, the most extensive work available up to 1965 was that of Raine and Bishop (1963). Using a stirred macro-cathode (see Chapter VI) they made duplicate measurements of arterial  $PO_2$  on 49 subjects, both male and female, and found a linear regression between arterial  $PO_2$  and age:-

$$\text{Arterial } PO_2 = 103.7 - 0.24 (\text{age in years})$$

with one standard deviation of their predicted value of 7.9 mm.Hg. The range 78 mm.Hg to 113 mm.Hg would appear to cover the mean values and one standard deviation about the mean in all their subjects. Cotes (1965) gives a normal range of 83 - 100 mm.Hg for arterial  $PO_2$  at 20 years of age, falling to 75-90 mm.Hg at age 60, apparently working from the figures of Raine and Bishop (1963). In 1952, Bartels and Rodewald published results of arterial  $PO_2$  measurements using the dropping mercury electrode, on 59 adult subjects, with a mean of 92.95 mm.Hg, standard deviation 5.71 mm.Hg, and a range of 80 - 104 mm.Hg. These were the best available figures at the time of compilation of the Biological Handbook "Blood and other Body Fluids" in 1961 (Altman and Dittner).

In 1965, Conway, Payne and Tomkin reported the arterial blood gas tensions in patients on a waiting list for surgery. The cardiovascular and respiratory systems of these patients were all normal, and they were all ambulant prior to the day of study. Arterial blood was sampled when the subjects were supine, and the  $PO_2$  was measured by an unstirred Beckman electrode, checked by "frequent tonometry". The results for oxygen tension

showed an inverse linear regression with age, of the form:-

$$\text{Arterial PO}_2 = 102.5 - 0.22 (\text{age in years})$$

with one standard deviation of 4.7 mm.Hg. The patients' ages ranged from 20 to 75 years. These figures would therefore appear to be the most reliable available for the normal arterial  $\text{PO}_2$  at the present time.

When the carbon dioxide tension of arterial blood is discussed, the method in most use today appears to be the Severinghaus electrode (Severinghaus and Bradley, 1958). The problem has been tackled with other methods for many years. Thus Gibbs, Lennox, Nims and Gibbs (1942), using the Henderson Hasselbalch equation, and measurements of total carbon dioxide content, and whole blood pH, by the glass electrode, on arterial blood in 50 supine subjects (age 18 to 29 years) found mean values of 39.9 mm.Hg, standard deviation 1.81 mm.Hg, and range 36.2 - 44.9 mm.Hg. Møller (1959) studied 100 normal subjects, 50 males and 50 females, aged from 20 - 60 years. He measured the carbon dioxide content and pH on plasma of arterial blood separated anaerobically at  $38^\circ\text{C}$ , and calculated the  $\text{PCO}_2$  values, using a pK value of 6.10. His mean for the men was 45.2 mm.Hg, standard deviation 2.4 mm.Hg and for the females mean 43.2 mm.Hg, with a standard deviation of 2.9 mm.Hg. One problem connected with such measurements is that arterial puncture can be slightly painful, even when using local anaesthetic, and most conscious patients have some reaction to the sight of their own blood literally spurting before their eyes. Hyperventilation due to anxiety is therefore very common in such normal subjects, and from my personal experience, this is more likely to be marked in medical subjects. It follows that the arterial  $\text{PCO}_2$



could therefore be too low. The simultaneous determination of arterial pH is a defence against errors from this cause, for if it is in the normal range, then it appears safe to assume that the arterial  $\text{PCO}_2$  has not changed rapidly, as for example following sudden hyperventilation from fright. In the work of Gibbs, Lennox, Nims and Gibbs (1942) the arterial pH was 7.42, with a range of 7.37 to 7.46, which is indeed a little high, suggesting therefore that their  $\text{PCO}_2$  values were too low. In Møller's work the mean pH was 7.37 in both males and females, with ranges from 7.33 to 7.41, which suggest hypoventilation, if indeed there was any abnormality. It will be apparent that this argument is, in fact, fallacious for it presupposes that the "true" normal arterial pH is known. Also as the  $\text{PCO}_2$  measurements were based on pH and carbon dioxide content values, pH and  $\text{PCO}_2$  values can scarcely be called independent.

An alternative approach is to use alveolar gas to measure  $\text{PCO}_2$ . This rests on the assumption that arterial  $\text{PCO}_2$  and alveolar  $\text{PCO}_2$  are identical in normal subjects breathing air at sea-level. This assumption, which cannot be tested experimentally with sufficient accuracy (see Chapter VI) lies at the heart of the model of the lung as a gas exchanger as proposed by Riley and Cournand (1951). The soundness of the concept is supported by a vast edifice of later work, and indeed most respiratory physiologists would not today challenge this view. It is essential to repeat that this concept is only proposed for normal subjects. If we accept the truth of this proposal, therefore, we can utilise information on alveolar  $\text{PCO}_2$  values, in normal



subjects, to answer the problem as to the normal level of arterial  $\text{PCO}_2$ . Using the Haldane-Priestley (1905) Alveolar Sampling Tube, Fitzgerald and Haldane (1905) obtained values for alveolar  $\text{PCO}_2$  in normal men and women (and in girls and boys) at Oxford. For men they found a mean of 39.2 mm.Hg, range 44.5 - 39.2 mm.Hg, and for women 36.3 mm.Hg, range 41.0 - 30.4 mm.Hg.

To return to the measurements on arterial blood, Raine and Bishop (1963) also measured the arterial  $\text{PCO}_2$  by modification of the interpolation technique (Astrup, 1956) in their 49 subjects. The values ranged between 41.7 and 32.6 mm.Hg. In addition to variations of methodology and those due to anxiety hyperventilation, the arterial blood gas tensions are affected by posture. Thus Bjurstedt, Hesser, Liljestr nd and Matell (1963) showed a fall of mean value 2.4 mm.Hg in both arterial  $\text{PO}_2$  and  $\text{PCO}_2$  when the subject stood, compared with the value when lying. The mean arterial  $\text{PCO}_2$  (supine) was 39.5 mm.Hg and arterial  $\text{PO}_2$  (supine) 92.6 mm.Hg., in five normal subjects.

Conway, Payne and Tomkin (1965) measured the arterial  $\text{PCO}_2$  by a Severinghaus electrode, in their 70 patients awaiting surgery. The patients were studied when lying supine and it will be recalled that they showed no abnormalities of the heart or lungs. There was no correlation with age as far as  $\text{PCO}_2$  was concerned, and no significant difference between the sexes. The overall mean arterial  $\text{PCO}_2$  was 38.6 mm.Hg, with a standard deviation of 3.1 mm.Hg.

### 3. Present Definition of Respiratory Failure:

It is of particular interest from the point of view of this study to ascertain the lower limit of arterial  $PO_2$  and the upper limit of arterial  $PCO_2$  which can exist in normal people, for these figures must determine the definition of respiratory failure. For both oxygen and carbon dioxide tension, the figures of Conway, Payne and Tomkin (1965) appear to be best, based as they are on modern electrode methods, and with the posture standardised, and a large number of subjects. If such criteria are used therefore and taking two standard deviations about the mean as defining the normal range, it would appear possible to define respiratory failure as follows:

Respiratory failure is present in a supine subject at rest, breathing air at sea-level, if because of impaired respiratory function, the arterial  $PO_2$  is below 75 mm.Hg or the arterial  $PCO_2$  is above 45 mm.Hg. If the arterial  $PO_2$  is low but the arterial  $PCO_2$  is below 45 mm.Hg the patient has respiratory failure of the first type; if both the arterial  $PO_2$  and the arterial  $PCO_2$  are beyond the limits stated, the patient has respiratory failure of the second type, or ventilatory failure.

### 4. Chronic Bronchitis and Emphysema:

The commonest condition causing respiratory failure of the second type, where hypoxia and carbon dioxide retention are combined, is chronic bronchitis and emphysema. This condition has proved difficult to define. In 1959 a Ciba Guest Symposium defined emphysema as "A condition of the lung

characterised by an increase beyond the normal in the size of the air spaces distal to the terminal bronchioles "either from dilatation or from destruction of their walls". The Symposium noted that chronic bronchitis was often used in Great Britain to denote cases that would be called asthma or emphysema in the United States.

Fletcher, Hugh-Jones, McNicol and Pride (1963) used radiological criteria to separate cases into three groups: chronic bronchitis, chronic bronchitis and emphysema, and emphysema without chronic bronchitis. A collaborative study on British and American patients (Burrows, Fletcher, Jones and Niden, 1964) lends some support to this classification. The essential pathological basis for these ideas has recently been provided by Burrows, Fletcher, Heard, Jones and Wootliff (1966). By multiple regression analysis, these authors found that the degree of emphysema (in terms of the Ciba Symposium definition) in whole lung sections (Gough and Whitworth, 1960; Heard and Isukawa, 1964) could be directly correlated with alteration of the peripheral vascular pattern in the chest X-ray, yet inversely correlated with the sputum volume and the  $PCO_2$ . Thus a patient with severe emphysema would have little sputum, and only a mild elevation of the arterial  $PCO_2$ , whereas a bronchitic (with a low emphysema "score" at post mortem) had much sputum and respiratory failure with a high  $PCO_2$ . In fact, severe emphysema alone is a relatively rare disease in Britain. In their original work, Fletcher, Hugh-Jones, McNicol and Pride (1963) could only find four such patients from the Bronchitis Clinic of the Hammersmith Hospital. This recent work is still controversial and some authorities feel that the separation may merely

be into mild and severe varieties of the same disease.

Nonetheless, if this analysis be accepted, it becomes apparent that respiratory failure of the ventilatory failure type is more commonly found in those patients who show little emphysema, in terms of an increase of size of the air spaces distal to the terminal bronchioles. The recognition of hypoxia combined with carbon dioxide retention, as shown by arterial blood analysis in chronic bronchitis, must be shared between Hoover (1913), Scott (1920) and Meakins and Davies (1925). In their book these latter authors describe five cases of emphysema (just to confuse the issue again) including two described by Scott. The carbon dioxide content of whole arterial blood varied from 55 to 75 mls/100 mls., and in three subjects the alveolar air, obtained by the Haldane-Priestley (1905) method, had a  $PCO_2$  of 44, 60 and 63 mm.Hg. Such samples in emphysematous subjects will not, in fact, be equal to the arterial values in either oxygen or carbon dioxide tensions.

##### 5. Oxygen Therapy in Chronic Respiratory Failure:

The pathogenesis of chronic bronchitis is poorly understood, but there appears to be general agreement that the primary abnormality is overproduction of mucous by the glands of the trachea and bronchi (Reid, 1963), which may result from atmospheric pollution (Report, 1963). Such excess mucous causes localised obstruction to small airways, and imposes great strain on ciliary movements. As a result infection, notably by *Haemophilus Influenzae* and the *Pneumococcus*, invades the bronchial tree, with widespread damage throughout the lung on a microscopical scale.



An exacerbation of such infection, therefore, further prejudices the efficiency of the lung in providing exchange of oxygen and carbon dioxide between gas and blood. The resultant acute exacerbation of respiratory failure is one of the most common medical emergencies in Great Britain. In this situation the arterial oxygen tension may fall to very low levels (Hutchison, Flenley and Donald, 1964). Treatment of this condition by administration of oxygen may be an urgent necessity. There is still no clear evidence as to levels of arterial  $PO_2$  which herald severe damage, but although opinions on this very difficult topic are not lacking (Campbell, 1965 a and b), support from hard scientific evidence is difficult to find. Refsun (1963) showed that the serum levels of enzymes released from the liver (serum glutamic oxaloacetic transaminase) rose dramatically when the arterial oxygen content fell below 9 mls./100 mls. blood (equivalent to a  $PO_2$  of about 30 mm.Hg) in patients with respiratory failure. He interpreted this to indicate that centrilobular liver cell necrosis occurred as the arterial  $PO_2$  fell to these low levels. In normal man a marked decline in mental powers occurs as the arterial (or alveolar)  $PO_2$  falls below 45 mm.Hg (Boycott and Haldane, 1908). Hoffman, Clark and Brown (1946) and Harboe (1957) found that consciousness is lost as the arterial  $PO_2$  falls below 30 mm.Hg. All these results refer to acute experimental hypoxia in healthy men. Such levels of arterial  $PO_2$  are therefore associated with considerable hyperventilation and resultant lowering of arterial  $PCO_2$ . This induces cerebral vasoconstriction, although the hypoxia tends to reverse this effect. However there seems little doubt that the cerebral blood

flow in normal subjects exposed to low oxygen partial pressures will be less than that found in bronchitic patients at comparable levels of arterial  $PO_2$ . It would therefore follow that the bronchitic will be more able to withstand a given degree of hypoxia, at least as far as the immediate cerebral effects are concerned, than will a normal subject.

The long-term effects of chronic hypoxia are undoubtedly serious. The mechanisms underlying the development of cor pulmonale (or right-sided heart failure) in patients with chronic respiratory failure are still debatable (Donald, 1963) and would merit a thesis unto themselves. They will not be discussed here. The major point in the present argument, however, is that patients with cor pulmonale have a lower mean arterial  $PO_2$  than patients with chronic respiratory failure who have not suffered from heart failure (Baldwin, Cournand and Richards, 1949; Platts, Hammond and Stewart-Harris, 1960; Aber, Bayley and Bishop, 1963).

If this evidence is accepted, then indeed hypoxia does "wreck the machinery as well as stop the machine" (Barcroft, 1920). It must follow that relief of hypoxia is urgently needed. The administration of oxygen in high concentrations in patients with "capillary bronchitis" was shown to lead to a fall in ventilation by Beddard and Pembrey (1908). Barach (1949) appreciated the dangers of uncontrolled oxygen therapy in such patients, and was the first to recommend that a gradual increase in oxygen dosage (given by a nasal catheter) might avoid the dangers of provoking mental deterioration in these patients. In 1949, Donald demonstrated that the descent into coma following oxygen therapy in such a patient was associated with a marked rise

in the arterial  $\text{PCO}_2$ . This finding was rapidly confirmed by Comroe, Bahnson and Coates (1950) who showed that changes in consciousness with oxygen only occurred if the arterial  $\text{PCO}_2$  before oxygen therapy was over 50 mm.Hg, if the arterial oxygen saturation was below 90% when breathing air, and if the oxygen therapy corrected the arterial hypoxaemia. Like Westlake, Simpson and Kaye (1955) they found a wide variation in the levels of arterial  $\text{PCO}_2$  and pH associated with unconsciousness. However in the latter study, all patients were unconscious if the  $\text{PCO}_2$  was over 120 mm.Hg and this is supported by later experience. Arterial  $\text{PCO}_2$  values of this level, however, are only encountered after injudiciously high levels of inspired oxygen concentration.

The central paradox of treatment of respiratory failure with carbon dioxide retention is now apparent; if patients with acute exacerbations of respiratory failure are severely hypoxic, how can this hypoxia be relieved without producing severe carbon dioxide retention and respiratory acidosis? Barach (1949) was well aware of the problem, and his scheme of gradually increasing the dosage of oxygen, administered by nasal catheter, was adopted in principle by Campbell (1960a). He introduced the Venturi oxygen mask (Campbell, 1960b) and claimed that by its use the inspired oxygen delivered to patients with respiratory failure could be controlled within  $\pm 1\%$ , in the range 21% to 35%. These claims were not supported by an investigation of the properties of this mask described by Flenley, Hutchison and Donald (1963), who introduced their own simple device (the Edinburgh oxygen mask) capable of controlling the inspired oxygen concentration within  $\pm 5\%$ . Later detailed study of controlled



oxygen therapy in ten patients led H Hutchison, Flenley and Donald (1964) to advocate a therapeutic crescendo in the treatment of these patients. In the first place they recommend that no more than 30% oxygen (2 litres/minute by an Edinburgh mask) be given to any patient where a clinical diagnosis of respiratory failure with carbon dioxide retention is made. In the second place, this clinical diagnosis can be confirmed by the determination of the mixed venous  $\text{PCO}_2$  by the rebreathing technique (Campbell and Howell, 1960). Finally, in any case where the  $\text{PCO}_2$  by the rebreathing technique is more than 70 mm.Hg, they suggest careful control of the blood gas tensions and pH obtained by repeated samples from a small indwelling nylon catheter introduced into the brachial artery by a modified Seldinger technique. Once such control on arterial blood is established, the aim should be to provide an arterial  $\text{PO}_2$  of above 50 mm.Hg and an arterial pH of above 7.25. If these limits, which represent an attempt to define the lighthouse marking the channel between the rocks of hypoxia and the reefs of respiratory acidosis, cannot be attained by conservative measures, then artificial ventilation by I.P.P.R. is indicated. The present author has substantiated this method of treatment by analysing the results in 50 patients treated along these lines (Flenley, 1966).

This digression into the problems of treating respiratory failure is justified, as the present investigation (as Chapter IV will show) arose as an attempt to study the abnormal behaviour of the mechanisms controlling respiration which must exist in these patients.



## CHAPTER III

### THE WORK OF BREATHING

The work of breathing may be defined as the work done by the respiratory muscles in order to ventilate the lungs. This subject has been studied sporadically over the years, but has still received less attention than other areas of respiratory physiology, such as gas exchange in the lung and the control of respiration. However in recent years there have been a number of publications on this subject, although it still

## CHAPTER III

remains, as Dill remarked in 1954, "one of the quieter areas of respiratory physiology". In this chapter, I will discuss the methods available for

measuring the work of breathing and the results obtained by application

### THE WORK OF BREATHING

of these methods to normal subjects and to patients with chronic bronchitis and emphysema.

#### Methods of Measurement: Oxygen Cost of Breathing:

There are two methods which measure the work of breathing. The first and older method was described by Lilljestr nd (1913). The method depends upon an accurate measurement of the total oxygen uptake by the lung, at various increased levels of pulmonary ventilation. If a graph of total oxygen uptake ( $\dot{V}O_2$ ) against minute volume of ventilation ( $\dot{V}_E$ ) is drawn, the relationship approximates to a parabola:-

$$\dot{V}O_2 = a + b(\dot{V}_E)^2$$

In this equation the value 'a' represents the total oxygen consumption at zero ventilation. This value, obtained by extrapolation, therefore,

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#### 1. Methods of Measurement: Oxygen Cost of Breathing:

There are two methods which measure the work of breathing. The first and older method was described by Liljestrand (1918). The method depends upon an accurate measurement of the total oxygen uptake by the body, at various increased levels of pulmonary ventilation. If a graph of total oxygen uptake ( $\dot{V}O_2$ ) against minute volume of ventilation ( $\dot{V}_E$ ) is drawn, the relationship approximates to a parabola:-

$$\dot{V}O_2 = a + b (\dot{V}_E)^2$$

In this equation the value 'a' represents the total oxygen consumption at zero ventilation. This value, obtained by extrapolation, therefore,

represents the oxygen consumption which does not arise from respiratory muscle activity. It will be apparent from this equation that a value of the "oxygen cost of breathing" can only be obtained by subtraction of a value of total oxygen consumption at a lower ventilation (Figure 2). Thus the oxygen cost of breathing only represents the value at the mean of these two known values. It will be apparent that this calculation assumes that a small portion of the parabolic relationship can be in fact represented by a straight line. This approximation becomes increasingly unsatisfactory as the distance between the two values of ventilation chosen for measurement of  $\dot{V}O_2$  are increased.

This method, although entirely sound in principle, suffers from grave practical disadvantages. They particularly arise from the very small value of the oxygen cost of breathing. As will be seen later, this amounts to between 0.5 and 2.0 mls. oxygen/litre of ventilation at resting ventilation, in normal subjects, or approximately 5% of the total resting metabolism. The measurement of such a quantity presents problems. By classical methods of open circuit indirect calorimetry, where oxygen consumption is calculated when breathing air by collection of the expired gas, the volume and oxygen concentration of which are measured, a small error in gas analysis can give totally erroneous results. For example:-

#### Oxygen Cost of Breathing

-If Lower Ventilation is 20 litres/min. STP.

Then if the inspired oxygen concentration = 20.94% (Air)

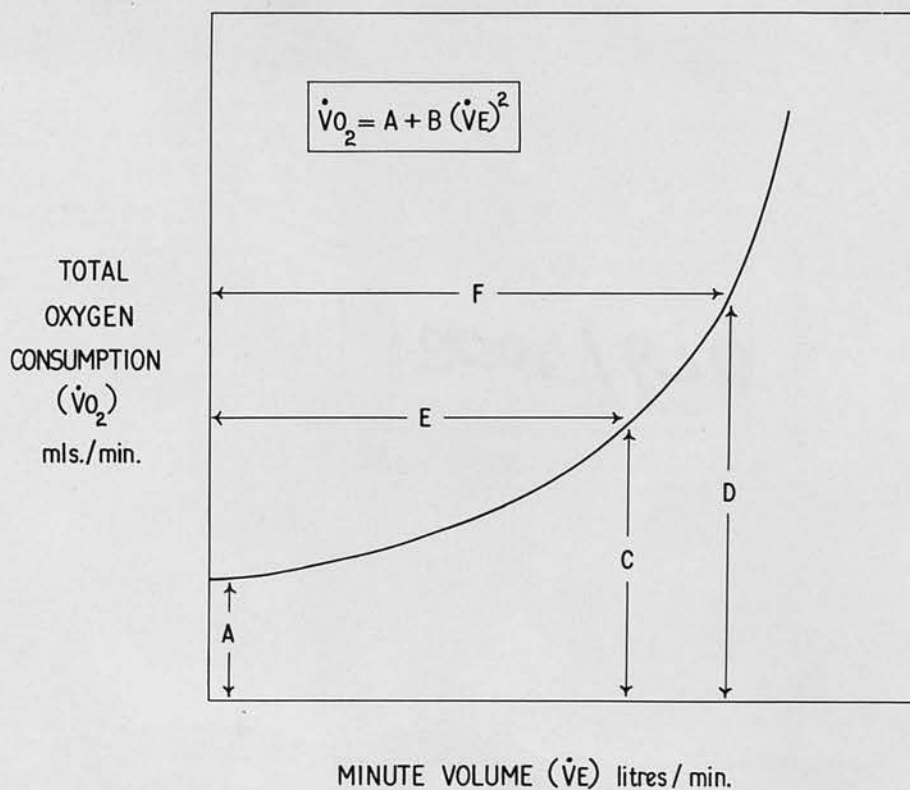


Figure 2

The measurement of the oxygen cost of breathing. For explanation of symbols see text. After Liljestrand (1918).



The total oxygen inspired is 4,188 mls S.T.P.

If the oxygen cost of breathing is 1 ml./litre. S.T.P. and the

basal oxygen consumption 250 mls. S.T.P.,

Then the total oxygen consumption at a Ventilation of 20 litres/min.

$$= 250 + (20 \times 1) = 270 \text{ mls. S.T.P.}$$

Therefore the total oxygen expired =  $(4188 - 270) = 3918$  mls. S.T.P.

But this is diluted in 20 litres of gas (if we assume an R.Q. of 1), so that the expired gas contains 19.59% oxygen.

By similar calculations it can be shown that the expired gas at a higher ventilation of 30 litres/min. contains 20.01% oxygen. If the ventilation measurement was in fact in error by 100 mls., and the gas analysis inaccurate by 0.03%, the final result, if these errors were in the worst direction, could be a negative value for the oxygen cost of breathing. This calculation has been considered at some length for it does illustrate clearly the intrinsic difficulties of this method. The experimental answer to such a problem, of course, is to refine the accuracy of the analytical methods, or to repeat the experiments sufficiently often to minimise such random variation in experimental error. This latter approach was used by Liljestrand, who repeated measurements on himself as a subject, in order to overcome this difficulty.

The problems of the method are not limited to those discussed above.

A basic principle in this method is the requirement that the basal oxygen consumption is constant, and that any extra oxygen intake is purely a result

of an increased oxygen consumption of the respiratory muscles. Such a situation is difficult to ensure in practice. In order to overcome the difficulties associated with gas analysis to such a very high degree of accuracy, Campbell, Westlake and Cherniack (1959) used a closed circuit, rebreathing from an oxygen filled spirometer, with carbon dioxide absorption, to measure both oxygen consumption and ventilation. They paid particular attention to comfort and maintenance of a constant position of their subjects. Campbell (personal communication) noted that crossing the legs during an experiment could completely ruin a measurement of oxygen cost of breathing by changing the basal oxygen consumption.

The final problem with this method lies in the method used to produce the increased ventilation. Liljestrand used voluntary hyperventilation but in addition to problems of changing body gas stores (particularly carbon dioxide) and R.Q., this method is very variable, except in trained subjects. The first difficulty can be avoided by adding carbon dioxide to the inspired gas as hyperventilation proceeds (Cournand, Richards, Bader, Bader and Fishman, 1954). However, a more elegant approach is to allow the subject to regulate his own breathing by merely adding an increased dead space (Campbell, Westlake and Cherniack, 1959). Cournand, Richards, Bader, Bader and Fishman (1954) studied one normal subject. They noted that the relationship between oxygen uptake and ventilation was indeed parabolic, and that oxygen uptake depended on respiratory rate as well as ventilation. For a ventilation of 25 litres above the resting level, the oxygen cost of

breathing was 1 ml. oxygen/litre, rising to 2 mls. oxygen/litre at a ventilation from 25 - 50 litres per minute. Again for normal subjects, Campbell, Westlake and Cherniack (1959) obtained mean values of 0.65 mls. oxygen/litre, rising to 1.2 mls./litre ventilation between 22 and 39 litres/minute. These results are the mean values in three normal subjects. Bartlett, Brubach and Specht (1958) studied two subjects over a total of 104 measurements at three breathing rates. They showed that the rate did not affect the result until a ventilation of over 70 litres/minute was achieved. They give no calculated results, and their figures are drawn to such a small scale that geometrical calculations are valueless. Milic-Emili and Petit (1960) studied four subjects but the detailed results are only given for one subject. At a ventilation between 20 and 40 litres/minute, this subject appears to have an oxygen cost of about 0.55 mls./litre of ventilation. A 200% variation in a measurement in normal subjects in the same age group (all subjects were 20 - 30 years old) would be unusual as a result of biological variation alone, and this would support the idea that such measurements by the Liljestrand technique are probably very inaccurate in normal subjects.

Before leaving this topic, however, it is only fair to point out that values of the oxygen cost of breathing in disease (Richards, Fritts and Davies, 1958; Campbell, Westlake and Cherniack, 1957) have revealed values very considerably higher than those found in normal subjects.

## 2. Methods of Measurement: Static Mechanical Properties:

Work is done when a force moves its point of application through a distance. In general, application of this simple physical definition to a biological system is fraught with hazard. For example no net work is done by a man walking along a level road, by the strict application of the above principle to the whole man. However the situation with regard to the respiratory system is not quite so puzzling. Air moves into the lungs, as a result of intercostal, diaphragmatic and accessory muscle contraction, which cause the volume of the thorax to increase. If the volume of the thorax, at any moment in the respiratory cycle, is plotted against the pressure differential which is causing the flow of air at that moment, a point is obtained on a pressure volume diagram. If the locus of that point is traced throughout the events of a respiratory cycle, a pressure volume "loop" is formed, enclosing an area. An area on such a diagram, representing as it does  $\int p. dv.$ , has the physical properties of work. So much is straightforward, but the identification of what work with what area is a little more complex.

If we consider the static pressure volume diagram of the thorax, representing volume on the vertical axis, and pressure on the horizontal axis (Figure 3), we may plot lines on this diagram which represent the relationships which may exist between the volume of gas in the chest, and the pressure differential across the structures containing that gas (Figure 4). If we regard all pressures as intrapleural pressure relative to atmospheric



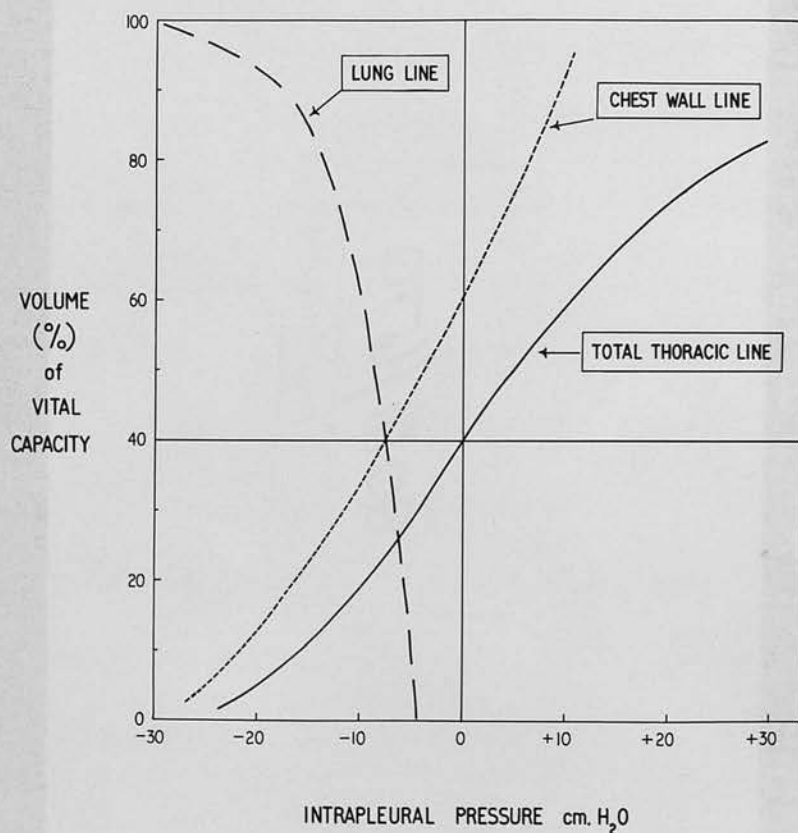


Figure 3

The static pressure/volume diagram of the lungs, chest wall, and whole thorax. The Campbell diagram, after Campbell (1958).

pressure the plot takes the form known as the Campbell diagram (Campbell, 1958) and this is done in fact in Figure 3. The solid line in this Figure (total thoracic line) represents the relationship existing between the differential pressure (between the airways and the atmosphere) and the lung volume, expressed as a percentage of vital capacity, during relaxation of all respiratory muscles. The origin of the graph, on the volume axis, is at the residual volume, the horizontal line is drawn at the functional residual capacity, or end tidal point, and the upper level of the volume axis is at the upper limit of the vital capacity. It is in fact a redrawing of the classic diagram of Rahn, Otis, Chadwick and Fenn (1946).

Also included on this diagram is the "lung line". This represents the relationship between the volume of gas in the lung, and the differential pressure between the pleural space and the airway, again during relaxation of the muscles. It is therefore the static lung compliance line. The final line, the "chest wall line" is the relationship between the volume within the thorax (or lung) and the differential pressure between the pleural space and the atmosphere, again during relaxation. This, therefore, is the chest wall compliance line. It is apparent that the algebraic addition of pressures from the lung line and pressures from the chest wall line at any given volume must in fact yield the pressures on the total thoracic line, at that volume.

This Figure 3, therefore, represents the static pressure volume relationships of the chest, all measured when the respiratory muscles are relaxed. This is usually done by asking the trained subject to inspire to

a given volume, and then keeping his mouth firmly applied to the mouthpiece, which is closed off by a tap from the atmosphere, to relax his respiratory muscles. The method was first used by Rohrer (1916) and rediscovered and developed by Rahn, Otis, Chadwick and Fenn (1946) and Fenn (1951) and has been extensively used by Heaf and Prime (1956), Agostoni and Rahn (1960), Naimark and Cherniack (1960), Mead (1961), Johnson and Mead (1963). The method is very dependent upon subject co-operation and even with trained and motivated normal subjects, Agostoni and Mead (1964) found that only one out of three subjects is capable of training to produce consistent results. The use of applied pressure to the system in order to change the volume within the thorax is only really valid over a small range of tidal volume, and not over the whole vital capacity. Agostoni and Mead again suggest that applied pressures of  $\pm 15$  cm.  $H_2O$  should not be exceeded if relaxation of the abdominal muscles at the end of expiration is expected. They based their conclusions upon electromyographic measurements during positive pressure breathing in a body plethysmograph, which is used to measure volume changes as a positive pressure is produced at the mouth.

In a thorough examination of the relaxation method of measuring the static mechanical properties of the thorax, divided into lung and chest wall components, Delhez, Troquet, Damoiseau and Petit (1963) concluded that the greatest experimental problem arose from the inconstant and incomplete provision of "relâchement des muscles respiratoires lors des manoeuvres de mesure utilisant la méthode de Rahn et coll. (1946)". The authors conclude

that results of such studies "doivent être considérées avec une prudence particulière". Although they only studied four subjects, these authors included electromyography of the diaphragm and the abdominal muscles in their measurements, and base their conclusions on such evidence. This work must command respect.

To overcome this difficulty, it is an obvious advantage to study anaesthetised subjects. Such studies are reported by Nims, Conner and Comroe (1955), Butler and Smith (1957), and Howell and Peckett (1957). The volume changes are slightly smaller for the same applied pressures under anaesthesia, which supports the idea that conscious subjects are incapable of complete relaxation. However all the anaesthetised studies refer to supine patients, except for two patients studied by Nims, Conner and Comroe (1955) who were in the lateral position for thoracotomy. As Agostoni and Mead (1964) show, the relaxation pressure volume diagram differs considerably between the upright (Rahn, Otis, Chadwick and Fenn, 1946) and supine posture, with a change of the resting end tidal point from just below 40% of vital capacity, when upright, to about 20% when supine. This change is associated with no change in the total thoracic compliance over the tidal volume range. Such a result would therefore support the idea that the "relaxing" subject can be induced to relax still more by anaesthesia or by paralysing his muscles.

### 3. Dynamic Mechanical Properties:

The above discussion is concerned with the static properties of the thoracic system, and apply only when there is no flow of gas into or out of



the system. These static properties are the elastic properties of the system. The present study is concerned with measurements of respiratory mechanical work, and these elastic forces described above are therefore but a part of the total work of respiration.

If we consider the work of inspiration only, this will include:-

- 1) Work done against elastic forces;
- 2) Work done against resistance to gas flow during inspiration  
(viscous work);
- 3) Work done against resistance to tissue deformation and in overcoming inertia of tissues, and accelerating tissues, during inspiration;
- 4) Work done on compressing alveolar gas during inspiration.

The work done against elastic forces can be measured on a static pressure volume diagram, as in Figure 3, if the tidal volume is known. If this tidal volume (Figure 4) be  $V$ , then the elastic work done on the lungs will be the area OAB in Figure 4. The elastic work done on the chest wall will, by analogy, be OBC.

If now we consider the viscous work, as under 2) above, this will be represented only on a dynamic pressure volume diagram (Figure 5). In this experimental record, the instantaneous pressure volume relationships across the lungs are displayed on the screen of an oscillograph, with volume on the vertical axis, and the differential pressure between the mouthpiece and intrapleural space (or oesophageal pressure, see later), on the horizontal axis.

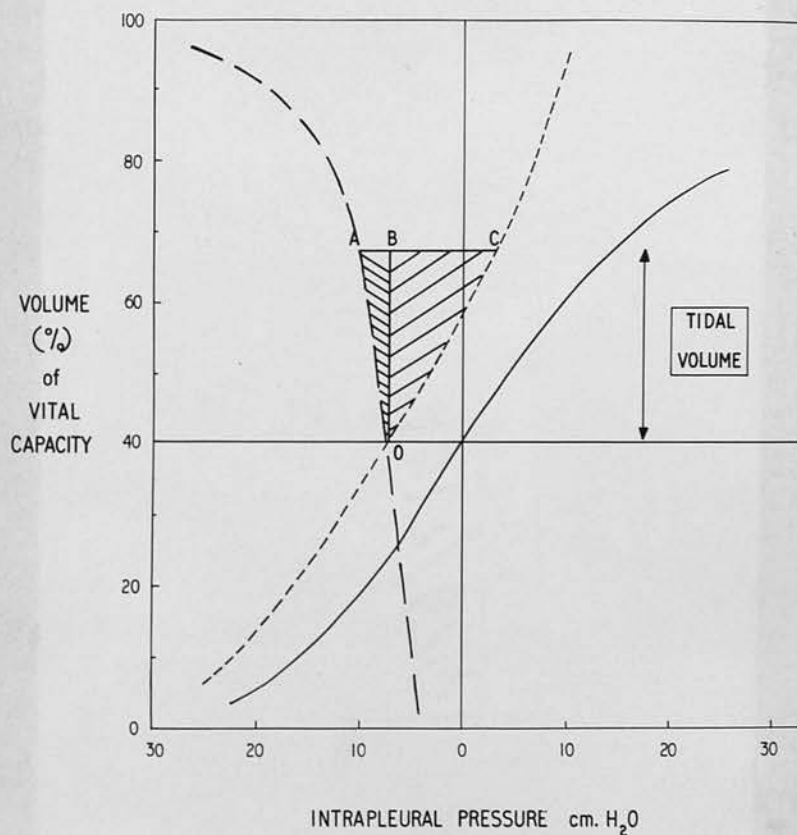


Figure 5

Dynamic pressure-volume diagram of the lungs. An experimental record, from an oscilloscope camera photograph, of a respiratory loop, with tidal volume on the y-axis and oesophageal to mouth pressure differential on the x-axis. The loop is interrupted for

Figure 4

The elastic work of inspiration on the lungs and on the chest wall. For explanations of symbols see text, The Campbell diagram.

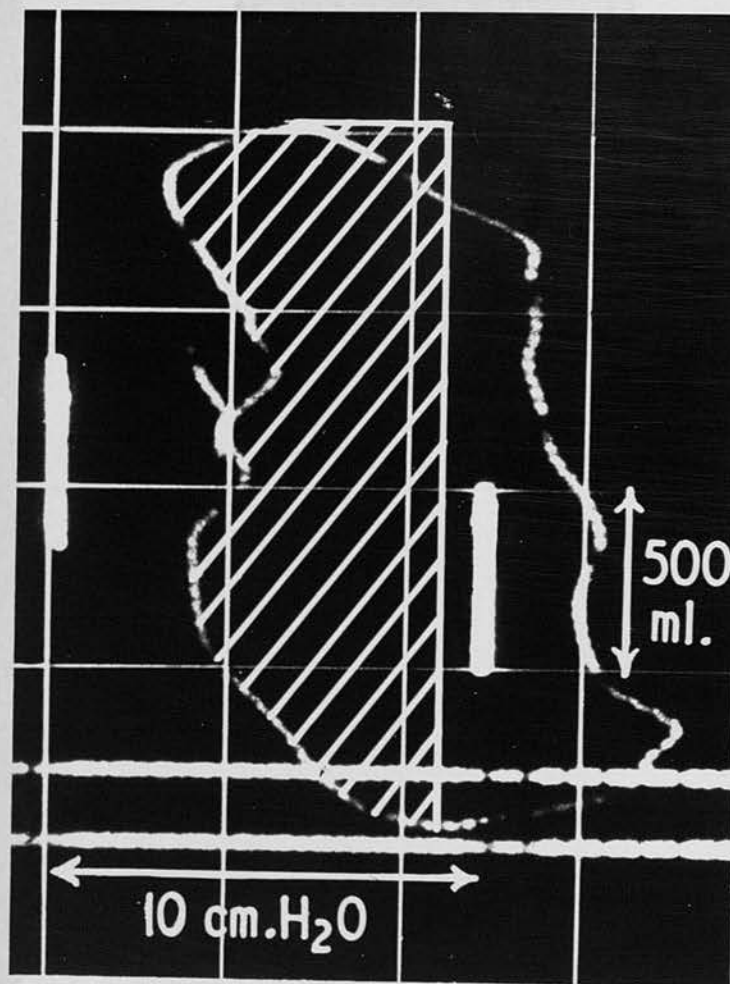


Figure 5

Dynamic pressure volume diagram of the lungs. An experimental record, from an oscilloscope camera photograph, of a respiratory loop, with tidal volume on the Y axis, and oesophageal to mouth pressure differential on the X axis. The loop is interrupted five times per second.

As the patient breathes in the left hand interrupted line is traced, until the top of the "loop" when expiration starts. The shaded area in Figure 5 represents the addition of the viscous and elastic work of breathing on the lungs.

The work done on the inertial forces and in providing acceleration of tissue, together known as the tissue viscous forces, has been found to be negligible at ordinary frequencies of breathing. I am incapable of following the methods and results upon which these conclusions are based, due to my lack of education in the physics of oscillating systems (DuBois, Brody, Lewis and Burgess, 1956). The work done on compressing the alveolar gas during inspiration, which is also not measured on the pressure volume diagram, discussed here, is also found to be negligible, provided that the respiratory rate is not very high. This result is based upon work on normal subjects and patients with American "emphysema" (Jaeger and Otis, 1964).

Finally, in consideration of the inspiratory work on a pressure volume diagram, the component due to compression of intra-abdominal structures must be considered. Agostoni and Mead (1964) point out that the abdomen and diaphragm are arranged mechanically in series with each other but in parallel with the upper ribs. This matter has not been considered in the results presented in this thesis; no doubt future studies will be required to elucidate the contribution of the individual components of chest wall work in patients with respiratory disease.



In summary, therefore, the conventional pressure volume diagram, including the static and dynamic components of work on the lungs, and static components for the chest wall, probably allows of measurement of the greater part of the work done in the individual breath. The difficult problem of variation in the end tidal point will be presented in Chapter IX.

#### 4. Measurement of the Intrapleural Pressure:

The method of measurement of the mechanical work of breathing, described above, requires that the pressure driving air into the lungs be measured during a breathing cycle. This pressure is, of course, the pressure differential between the mouth and the pleural surface of the lungs.

The obvious method of measuring this pressure is to introduce a needle into the pleural cavity after induction of a small pneumothorax. This was the method originally used by Neergard and Wirz (1927). The disadvantages of this method are numerous. They include the pain of needling (which is apparently not overcome even by intercostal block, Daly and Bondurant, 1963), the danger of producing rupture of the lung, and difficulties from blockage of the recording catheter by blood clot. The introduction of an indirect measurement of intrapleural pressure, by use of the intraoesophageal pressure, was therefore a significant advance (Buytendijk, 1949). The technique most frequently used is to place an air-filled tube, covered by a thin walled balloon, in the lower portion of the oesophagus. The details of balloon, and of its position, have varied widely.

Direct comparisons between the pressure recorded by a balloon in the lower third of the oesophagus and a pressure recorded from the intrapleural space have been made in man by Fry, Stead, Ebert, Lubin and Wells (1952), Cherniack, Farhi, Armstrong and Proctor (1955), Butler, White and Arnott (1957), Mead and Gaensler (1959), and Daly and Bondurant (1963). Without giving details of all these studies, it seems fair to summarise the conclusions. Provided that the subject is sitting or standing, but not lying supine, the intra-oesophageal pressure will reflect changes in the intrapleural pressure with considerable accuracy, except possibly at the extremes of vital capacity, but it is considerably less accurate as a guide to absolute values of intrapleural pressure.

As mentioned earlier, the actual technique of recording the intra-oesophageal pressure has varied somewhat. The position has been summarised by Dr. Milic-Emili in a personal communication (1965) to the author as "This is an art, not a science". As Dr. Milic-Emili has done more work in this field recently than anyone else, his views must command attention. Mead and Whittenberger, in an important paper in 1953, described a balloon 3 cms. long, and of volume 1.5 mls., when undistended, sealed to a polyethylene tube 25 inches long, and 1 mm. i.d. with spiral holes in the portion covered by the balloon. They showed that the least scatter in values of lung dynamic compliance (and resistance) measured during spontaneous respiration, were obtained if the balloon was situated in the lower third of the oesophagus, in seated subjects. The technique was further studied by Mead, McIlroy,

Silverstone and Kreite (1955), who compared the values of compliance obtained with a short (3 cm.) and long (16 cm.) balloon. They found much less variation in values using the longer balloon, and therefore recommended this method.

Milic-Emili, Mead, Turner and Glancer, in 1964, re-examined this whole problem. They pointed out that the pressure within the balloon will be the same as the local pleural pressure only if the pressure difference across all intervening structures (balloon wall, oesophageal wall, and various mediastinal structures) is zero. The difficulty of equating balloon pressure with absolute intrapleural pressure, noted above, results from the distortion of these surrounding structures that must occur in the balloon is distended with an appreciable volume of gas. As a result of their study on eight healthy men during breath-holding (relaxation pressure volume curves of the lung) they conclude that measurements are best made at very small volumes of gas in the balloon, which measured 10 cm. in length, and had a perimeter of 3.5 cm. The balloon was placed with its tip at 45 cms. from the nares which would mean that it lay in the lower third of the oesophagus. Again it is to be emphasised that the balloon volume was only of importance in determining the absolute accuracy of the intrapleural pressure measurements, and an increase in balloon volume from 0.2 to 4.0 mls. made very little change in the relative pressure changes at various lung volumes, provided that the extremes of vital capacity were avoided.



Unfortunately, the present study was well under way before this paper of Milic-Emili and his colleagues was published in 1964. The most recent work on this problem at that time was that of Petit and Milic-Emili (1958). These authors then claimed that "only measurements made with balloons having perimeters greater than 4.8cms. express the mechanical properties of the esophageal walls". When referring to the error in assuming that the endoesophageal pressure variation was equal to the true intrathoracic pressure variation, they state "when utilizing balloons 15 cm. in length and 5 cm. in perimeter, introduced into the lower portion of the esophagus, the error becomes negligible". This was the technique used in the present study.

The use of a long balloon was held to have the advantage that it provides a mean value for the intrathoracic pressure. It is obvious that the intrapleural pressure relative to atmosphere will in fact vary from point to point down the lung, in the upright posture. This has been shown to occur experimentally by Daly and Bondurant (1963), the differences between two sites in the pleura vanishing when a pneumothorax was induced. They point out that such local pressure differences (a higher pressure at the bottom than at the apex of the lung) suggest either that the lower zones of the lung are less compliant, or that the upper zones receive less tidal volume. As they point out, this latter suggestion is in contradiction to the greater distribution of air flow to the upper zones of the lungs as described by West (1965), and therefore they conclude that the lower lung areas are less compliant. Such regional variation in lung mechanical properties does not invalidate measurements





applied to the whole lung, provided that the intraoesophageal pressure, measured over a long balloon in the lower third of the oesophagus, does in fact measure the mean intrapleural pressure. The weight of evidence from the work reviewed would suggest that such is indeed the case.

#### CHAPTER IV

#### THE PURPOSE OF THE PRESENT STUDY

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The previous three chapters have summarized the background to the present problem: the first describing the evolution of modern ideas on the chemical regulation of respiration; the second on the abnormalities of respiratory regulation which are found in respiratory failure, and in the chronic bronchitic who gives oxygen to breathe; the third on methods of measurement of ventilation.

## CHAPTER IV

The present chapter aims to synthesize these ideas into a statement of the aims of the present study. This may briefly be given as:

### THE PURPOSE OF THE PRESENT STUDY

To study the abnormalities of respiration which occur in patients with chronic ventilatory failure.

#### 1. Ventilatory Response to Carbon Dioxide in Respiratory Failure:

The patient with ventilatory failure has a low arterial  $PO_2$  and a high arterial  $PCO_2$ , by definition, and one would predict that his breathing would therefore be stimulated by this potent combination of chemical factors. The persistence of such an abnormality in blood gas tensions therefore implies that his response to chemical stimulation is abnormal. In what way is it abnormal? Does the understanding of the abnormality throw any light on the normal regulation of ventilation, or upon the correct way to treat such patients?

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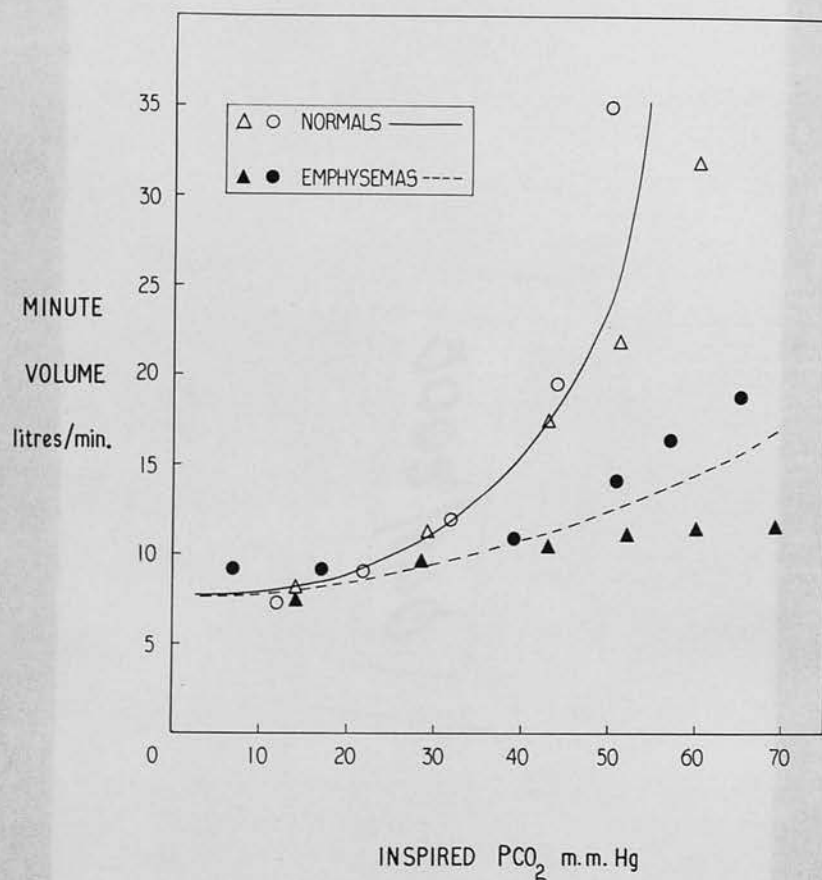
To study the abnormalities in the chemical control of respiration which occur in patients with chronic ventilatory failure.

#### 1. Ventilatory Response to Carbon Dioxide in Respiratory Failure:

The patient with ventilatory failure has a low arterial  $PO_2$  and a high arterial  $PCO_2$ , by definition, and one would predict that his breathing would therefore be stimulated by this potent combination of chemical factors. The persistence of such an abnormality in blood gas tensions therefore implies that his response to chemical stimulation is abnormal. In what way is it abnormal? Does the understanding of the abnormality throw any light on the normal regulation of ventilation, or upon the correct way to treat such patients?

The problem posed by the existence of ventilatory failure is usually answered by "decreased sensitivity of the respiratory centre". I do not find this an intellectually satisfying answer. One of the first workers who also felt the challenge of this problem was Scott (1920). He measured the alveolar carbon dioxide tension, by the Haldane-Priestley method, and noted that patients with emphysema (of the "large-lunged type"), "may be comfortable and able to walk about whilst tolerating in the alveolar air a percentage of carbon dioxide (sic) which would cause a profound hypernoea in a normal person". He studied two cases of emphysema, and compared the results with those of similar experiments in two normal subjects. His results are shown in Figure 6, redrawn from his tables, and expressed in terms of the inspired  $\text{PCO}_2$ , assuming a barometric pressure of 760 mm.Hg. In this paper Scott also described the determination of the mixed venous  $\text{PCO}_2$  by the rebreathing technique, and used the results to confirm his findings from alveolar samples, namely that the arterial  $\text{PCO}_2$  was increased in such patients. He also determined the total carbon dioxide content and pH of directly sampled arterial blood, and demonstrated that although the arterial carbon dioxide content was greatly increased in emphysema, the arterial pH was almost normal. He went on to attribute the decreased sensitivity to both inspired carbon dioxide and the raised arterial  $\text{PCO}_2$  as ventilatory stimulants to the increased buffering in the arterial blood which these findings revealed. This idea was, of course, completely in line with the original formulation of Winterstein's Reaction





**Figure 6**

The relationship between minute volume and inspired  $\text{PCO}_2$  found by Scott (1920) in normal subjects and emphysema patients. Redrawn from results given by Scott (1920).

Theory (1911) which attributed all chemical respiratory drive to the acidity of the arterial blood.

The later developments of the Reaction Theory (Winterstein, 1921; Gesell, 1925) with the concept of the acidity within the respiratory centre as the unique ventilatory drive, were also in keeping with Scott's findings, for surely the "cell fluid" of the centre would behave in the same manner as the blood. If the one showed an increase in buffering surely this could also occur in the cells. Indeed it could, for almost nothing was then known (and very little now) about acidity regulation within the cell during chronic elevations of arterial carbon dioxide tension. This is at once both the ingenuity and challenge of the modern Reaction Theory; how is it to be tested?

The diminished ventilatory response to carbon dioxide inhalation in such patients was confirmed by Donald and Christie (1949) whose results in some patients suggested that prolonged inhalation (over 20 minutes) of carbon dioxide mixtures may produce a greater ventilation than that occurring after ten minutes. Prime and Westlake (1954) re-examined the problem, and pointed out that hyperventilation from carbon dioxide resulted in a rise in arterial  $PO_2$  as well as arterial  $PCO_2$ , in these hypoxic patients. In six patients, the arterial  $PO_2$  rose between 20 and 29 mm.Hg when 7% carbon dioxide in air was given. They therefore conducted their experiments with carbon dioxide mixtures made up in oxygen in order to study the changes due to carbon dioxide alone. This

approach, unfortunately, begs quite a few questions. It does not allow any study of the interactions between hypoxia and hypercapnia, as respiratory stimulants. The ventilatory depressant effect of high concentrations of oxygen has already been noted in Chapter II, and indeed it is therapeutically the most immediately relevant problem. It seems not impossible that a rise in  $\text{PCO}_2$  may produce a different ventilatory response when given in association with a ventilatory depressant. Despite these strictures, the study of Westlake and Prime was important in demonstrating that the ventilatory response to a rise in arterial  $\text{PCO}_2$  was inversely related to the resting level of arterial  $\text{PCO}_2$ . It was also the first study to report results in terms of the arterial  $\text{PCO}_2$  and not merely the inspired concentration.

## 2. The Response to Carbon Dioxide Inhalation in Terms of the Work of Breathing:

These observations left the problem essentially unanswered; indeed Prime and Westlake conclude their summary with "the major factor is, in all probability, an alteration in the sensitivity of the respiratory centre". In 1958, however, Richards, Fritts and Davies presented a new concept to the Association of American Physicians. They pointed out that the depressed carbon dioxide response in emphysema could arise from "the increased effort required to ventilate the lungs". They go on "The ideal way to study the performance of the respiratory centre would be to apply a stimulus of known intensity, and then to measure the number of nerve impulses which

the stimulus would produce". If the stimulus be represented by the arterial  $\text{PCO}_2$  (vide infra), then the problem is to identify, and measure, the response. The total nervous impulse output is obviously not measurable in man, yet they proposed that as an alternative to measuring ventilation as the response, measurements of the "extra energy utilized by the respiratory muscles" could be used. Figure 7, adapted from their paper, illustrates the idea. The left-hand box, containing the respiratory centre, efferent nerve and muscles, is stimulated by the effect of a rise in arterial  $\text{PCO}_2$  on the central and peripheral chemoreceptors. The output of this left-hand box acts on the right-hand box (chest bellows and lungs) to produce the observed ventilation. They argue that a measurement of the output of the left-hand box is the oxygen cost of breathing. Thus "the performance of the left-hand box is characterised by determining the extra energy utilized by the respiratory muscles for a particular increment in the arterial blood  $\text{PCO}_2$ ; the performance of the right-hand box is characterised by measuring the extra ventilation realised per increment of energy consumed".

They applied this reasoning to measurements of oxygen uptake at each level of breathing as ventilation increased during the inhalation of 0 - 7% carbon dioxide in eight normal subjects, and from 0 - 5% in nine patients with emphysema. Results were expressed in terms of oxygen uptake per unit surface area, plotted against the arterial  $\text{PCO}_2$ . Despite considerable variation between individuals the results in the two groups,



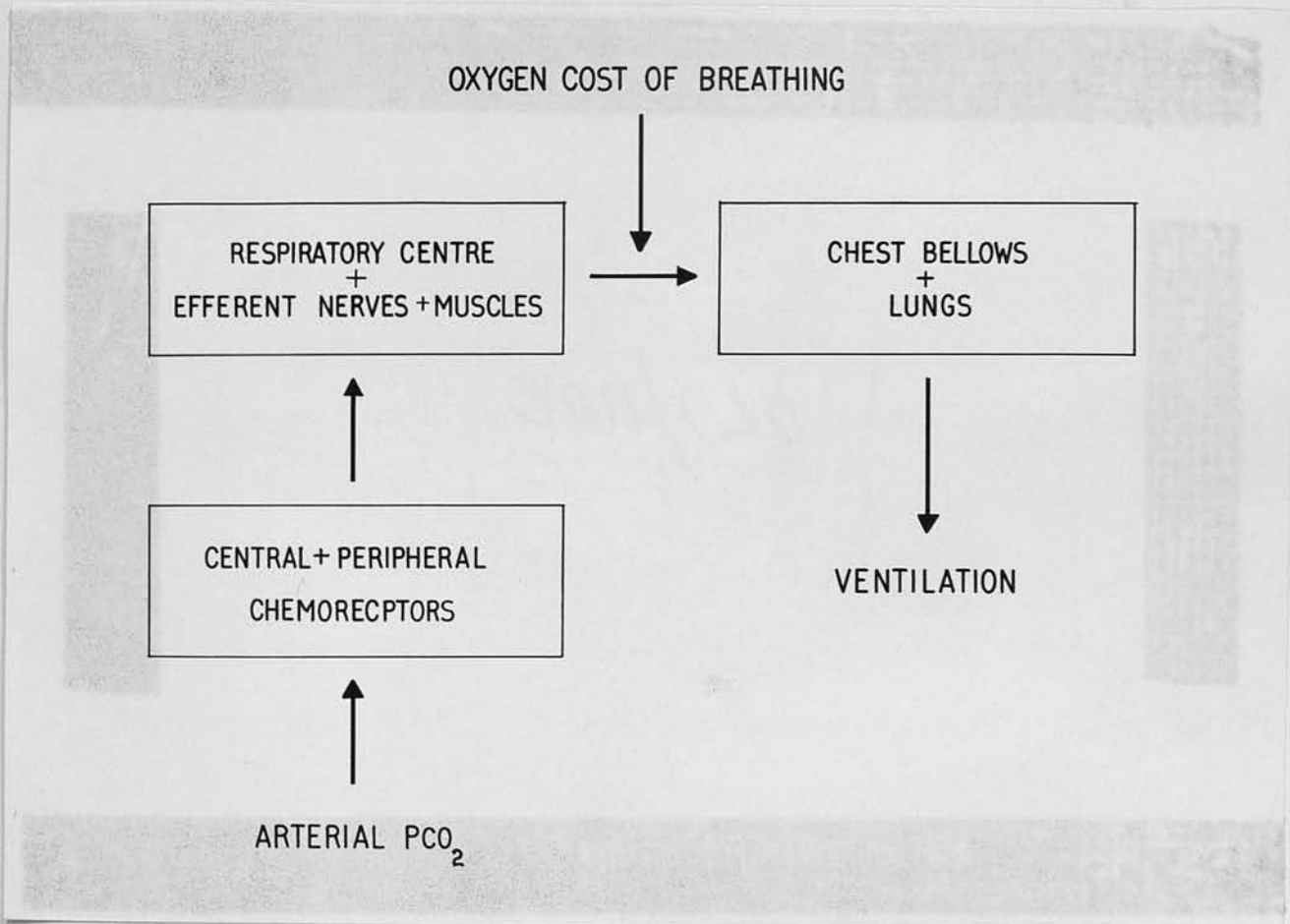


Figure 7

The rationale of measurement of the oxygen cost of breathing, and its theoretical relationship to ventilatory control. Redrawn from Richards, Fritts and Davies (1958).

normal subjects and emphysema patients, were remarkably similar in the slope of the relationship. Yet when the same results were plotted in terms of the ventilatory response to the rise in arterial  $\text{PCO}_2$ , the results were totally different. The authors therefore concluded "the data indicate that the altered mechanical properties of the lungs play an important role in reducing the response to carbon dioxide in this particular group of patients with emphysema. By way of contrast, the response of the respiratory centre and the muscles, measured in terms of effort, appear to be similar in the normal and in this patient group".

Exactly the same chain of reasoning was used by Brodovsky, MacDonnell and Cherniack (1960), who also concluded that the response of the respiratory muscles would be a more accurate measurement of respiratory centre output than measurements of the ventilation alone. Again these authors measured the oxygen cost of breathing, but in addition they calculated the mechanical work done by those muscles, from estimates of the efficiency of the respiratory muscles. They studied 12 normal subjects and 10 patients with emphysema. The method was that described by Campbell, Westlake and Cherniack (1957), as was used in normal subjects by Campbell, Westlake and Cherniack (1959). This method depends upon measurements of oxygen cost by rebreathing from a closed circuit, which is filled with oxygen and where the carbon dioxide is absorbed. The studies were therefore carried out when breathing very high concentrations of oxygen. In all the emphysema patients high oxygen levels produced

hypercapnia and all were hypoxic when breathing air at rest. Thus, inevitably, the experiments must have both added carbon dioxide and removed hypoxia, a double stimulation experiment, similar in that respect to the work of Prime and Westlake. Increase in ventilation in this system was produced by interposing various amounts of dead space. The method of Liljestrand (1918) was used to calculate the oxygen cost of increased ventilation, from plots of ventilation against oxygen consumption. The efficiency of the respiratory muscles was measured by comparing the oxygen cost of breathing, at a given ventilation, with "the oxygen cost at the same ventilation, when in addition a calculable amount of external work was done against an external resistance". The authors claimed that the efficiency of the respiratory muscles had been shown to be constant at different levels of ventilation (Campbell, Westlake and Cherniack, 1957), and therefore felt justified in using their efficiency factor to convert the measured oxygen cost of breathing into mechanical efficiency values, at various levels of ventilation, for each subject. The final results, therefore, are presented as plots of mechanical work against arterial  $\text{PCO}_2$ . In these terms, the results show unequivocally that the response in terms of an increase in mechanical work, is much less in the patients with emphysema than in the normal subjects (Figure 8).

It will be apparent, therefore, that these results are in contradiction to those of Richards, Fritts and Davies (1958). Such a conflict requires resolution. It seems imperative to examine the methods in detail.

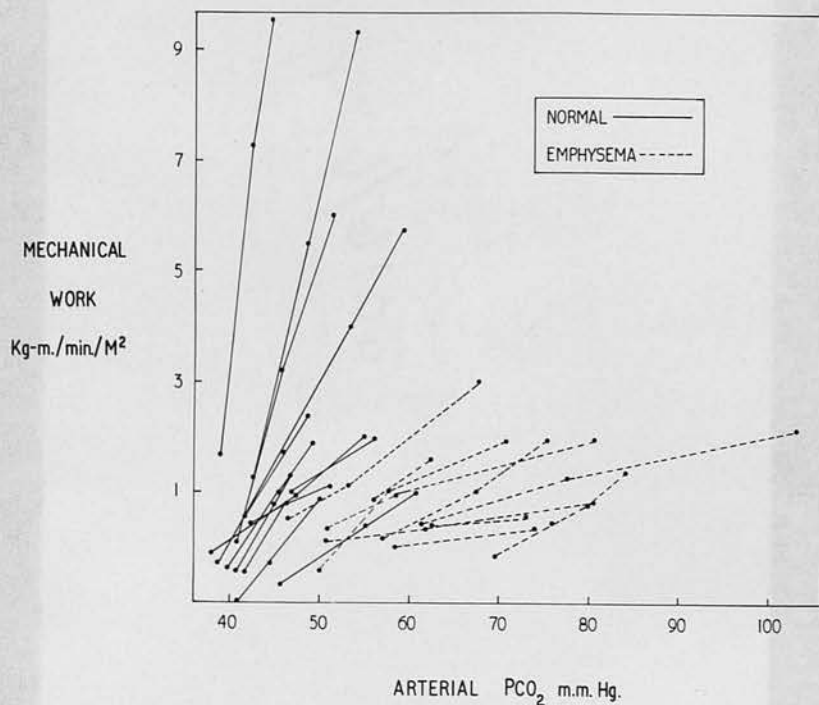


Figure 8

The relationship between the mechanical work of breathing and the arterial  $PCO_2$ , as found by Brodovsky, MacDonnel and Cherniack (1960). Redrawn from that paper.



Unfortunately, Richards, Fritts and Davies do not describe their methods in detail, but apparently used those described by Cournand, Richards, Bader, Mortimer and Fishman (1954). In that study the oxygen cost was calculated from measurements of oxygen concentration and ventilation, whilst the subject inhaled carbon dioxide mixtures in air. The discussion of errors in Chapter III would suggest that this method may well have led to erroneous results, for the inspired gas did not contain a standard known amount of oxygen (as does air), and a double analytical error would therefore be possible.

On the other hand, although the basic measurements of oxygen consumption of Brodovsky, MacDonnell and Cherniack were probably more accurate, the calculation of the mechanical efficiency of the respiratory musculature appears rather doubtful.

The method can be described as follows:

If  $\dot{V}_E$  = minute volume

$\dot{V}_{O_2}$  = oxygen consumption

$K_1$  = a constant for any given patient,

Then, if  $\dot{V}_E = K_1 \dot{V}_{O_2}$  ... (1)

and  $\dot{V}_{O_2} = K_2$  (Mechanical work) ... (2)

Where  $K_2$  = efficiency, and if  $K_2$  is independent of  $\dot{V}_E$  (as Campbell, Westlake and Cherniack, 1957, claim),

Then, by substitution:

$\dot{V}_E = K_1 K_2$  (Mechanical work) ... (3)

Again, as  $K_1$  and  $K_2$  are constants, and as the response of bronchitic patients to a rise in  $\text{PCO}_2$  is known to be depressed, when expressed in terms of ventilation, it follows that the response will also be depressed in terms of mechanical work, for by their reasoning mechanical work and ventilation are made to be related in a linear fashion (equation 3).

The reason for this result would appear to lie in the fallacy of equation (1).

$$\dot{V}_E = K_1 \dot{V}_{O_2}$$

This is, of course, not true, as Liljestrand's work originally showed.

Thus:

$$\dot{V}_{O_2} = K_3 (\dot{V}_E)^2$$

It is true that over short sections of this parabolic relationship the linear approximation of equation (1) is adequate, but it seems rather unwise to base the main conclusions of the paper on this basically untrue approximation. The external resistance used by these authors to measure the efficiency of the respiratory muscles is so constructed (a pipe projecting under water) that the pressure drop remains constant at a wide range of flow rates. Thus the rate of doing work on this resistance is  $\dot{V}_E \cdot P$ , where  $P$  is the pressure drop, which is independent of  $\dot{V}_E$ . Thus the work rate is a linear function of  $\dot{V}_E$ . As however the oxygen cost of breathing is related to  $\dot{V}_E$  by a parabolic relationship, it appears that the respiratory system behaves differently, in so far as its own work response to an increase in ventilation is concerned, to that work done on the external resistance.

These points have been discussed in some detail for they do in fact

reveal the need for this problem to be studied from a fresh viewpoint with alternative methods of measuring the work of breathing.

### 3. The Questions Posed in the Present Study:

The position with regard to the present study can now be explained more fully. This study tried to provide answers to the following questions:-

1. What is the relationship between the arterial  $\text{PCO}_2$  and the ventilation during steady state measurements in normal subjects and patients with varying degrees of hypoxia and hypercapnia, when breathing air?
2. Can the differences in this response to carbon dioxide be explained in terms of increased buffering capacity of the arterial blood?
3. Can the difference in response be explained in terms of the difference in mechanical work of breathing?
4. What is the effect of variation in arterial oxygen tension upon the ventilatory response to carbon dioxide in chronically hypoxic patients?

These were the primary questions at the outset, but as the study proceeded, it became apparent that additional questions were relevant, and could be answered from the results obtained.

5. What are the differences in acid base balance of the blood during carbon dioxide inhalation between normal subjects and patients with chronic hypercapnia?
6. What is the relationship between ventilation and viscous work of breathing in normal subjects and in patients with chronic airways obstruction?

The following chapters will describe the experiments designed to answer these primary questions, and the results obtained, and in discussion the secondary questions will also be considered.

## CHAPTER V

### METHODS



## CHAPTER V

### METHODS

The aims of this study, as discussed in the last chapter, required that the response to experimental increases in arterial  $PCO_2$  should be measured, in terms of minute volume of ventilation and respiratory work, in both normal subjects and patients with chronic bronchitis and emphysema.

### CHAPTER V

In addition, the arterial  $PCO_2$  should also be changed in order to study the interaction of carbon dioxide and oxygen as chemical stimulants to respiration. The problems to be solved were therefore:-

#### METHODS

1. Design of an experimental procedure;
2. Measurement of the minute volume of ventilation;
3. Measurement of the inspiratory work on the lungs and on the chest wall;
4. Measurement of arterial blood gas tensions and pH.

The first three problems will be considered in this Chapter, the measurement of arterial blood gas tensions being considered separately in Chapter VI.

#### 1. Design of the Experimental Procedure:

One of the main sources of this study has been the work of the Oxford School (Lloyd, Jukes and Cunningham, 1956; Cunningham, Shaw, Leibel and Lloyd, 1961) on the relationship between ventilation and alveolar gas pressures in normal man. The procedure adopted was therefore

## CHAPTER V

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based upon their methods. The subjects were given nine different inspired gas mixtures to breathe (exact details are given in the results section) which were designed to produce three different levels of arterial  $PO_2$ . These mixtures were so combined as to attempt to obtain the "isoxic" respiratory response to carbon dioxide. By this term is meant the response to three different levels of arterial  $PCO_2$ , all at same level of arterial  $PO_2$ , this pattern then being repeated to study two other levels of arterial  $PO_2$  at each of which the response to three levels of arterial  $PCO_2$  was measured. One inspired gas mixture was given continuously for at least 15 minutes before any measurements were made. From preliminary work it was found that rapid reduction in the arterial  $PCO_2$ , by returning the subject rapidly to air after a high carbon dioxide mixture, could often cause severe headache, and sometimes nausea and vomiting. The gas mixtures were therefore given in a standard order, of three levels of oxygen with no carbon dioxide added to the inspired gas, at three levels of oxygen at high carbon dioxide levels, and finally three levels of oxygen with intermediate carbon dioxide levels. The protocol is illustrated in Figure 9.

The three levels of oxygen refer of course to the levels in the arterial blood. In all subjects it was intended to produce arterial  $PO_2$  levels of about 50 mm.Hg, 90 mm.Hg and 140 mm.Hg, with arterial  $PCO_2$  levels at the resting value, with increments of about 5 and 10 mm.Hg in the other periods. The results show that these aims were certainly not

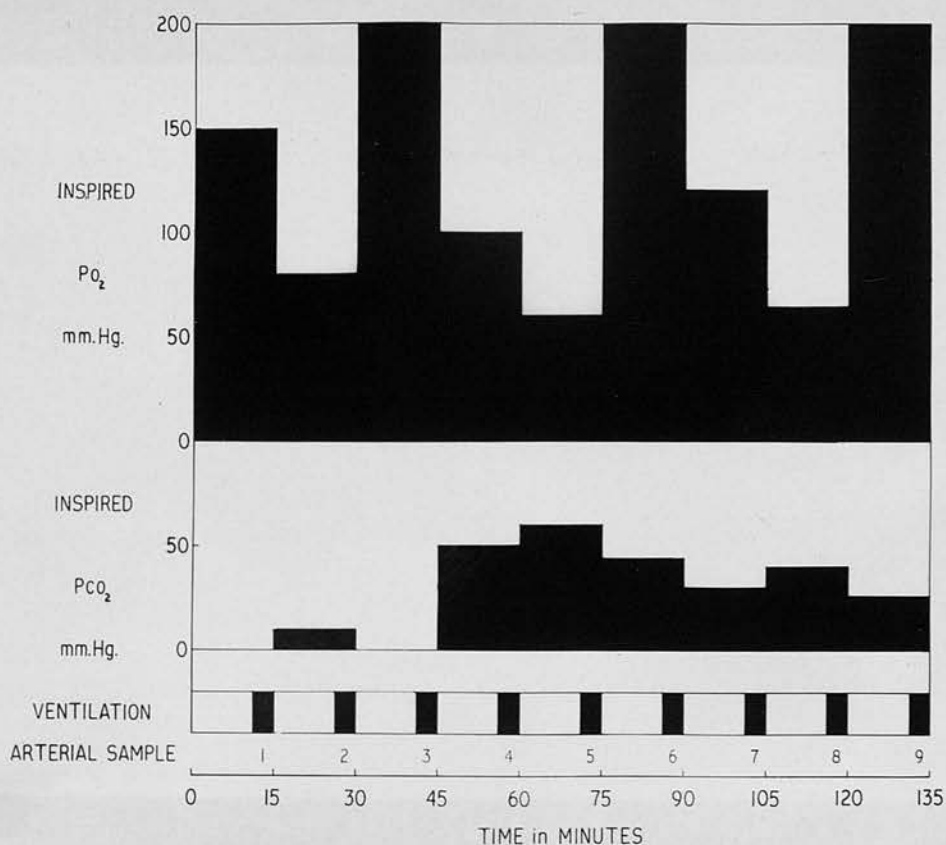
achieved with the accuracy which was intended originally, but the reasons for these deficiencies are discussed in Chapter VII. From Figure 9 it will be noted that some extra carbon dioxide was in fact added to the inspired gas during the first period of hypoxia. This was done in order to prevent the hypoxic hyperventilation resulting in a fall much below resting values, in the normal subjects, for the linear relationship between ventilation and arterial (or alveolar)  $\text{PCO}_2$  levels, which is described by Nielsen and Smith (1951) and by Lloyd, Jukes and Cunningham (1958), only obtained for values of  $\text{PCO}_2$  above the resting level.

## 2. Measurement of Minute Volume:

The method adopted was unconventional and requires explanation. As will be seen the patients selected for this study included those with severe ventilatory failure due to chronic bronchitis and emphysema. Such patients are notoriously intolerant of mouthpieces and valves, or indeed of any resistance to either inspiration or expiration. In addition it was desired to obtain a continuous analogue record of tidal volume, in order to display this on the volume axis of a pressure volume plot, for the computation of respiratory work.

It was accordingly decided to use a pneumotachygraph to record instantaneous values of air flow, and then to integrate the flow signal thus obtained, with respect to time, and thereby obtain the required continuous electrical analogue signal of the tidal volume. This procedure was adapted from that of Mead and Whittenberger (1953). The use of a





**Figure 9**

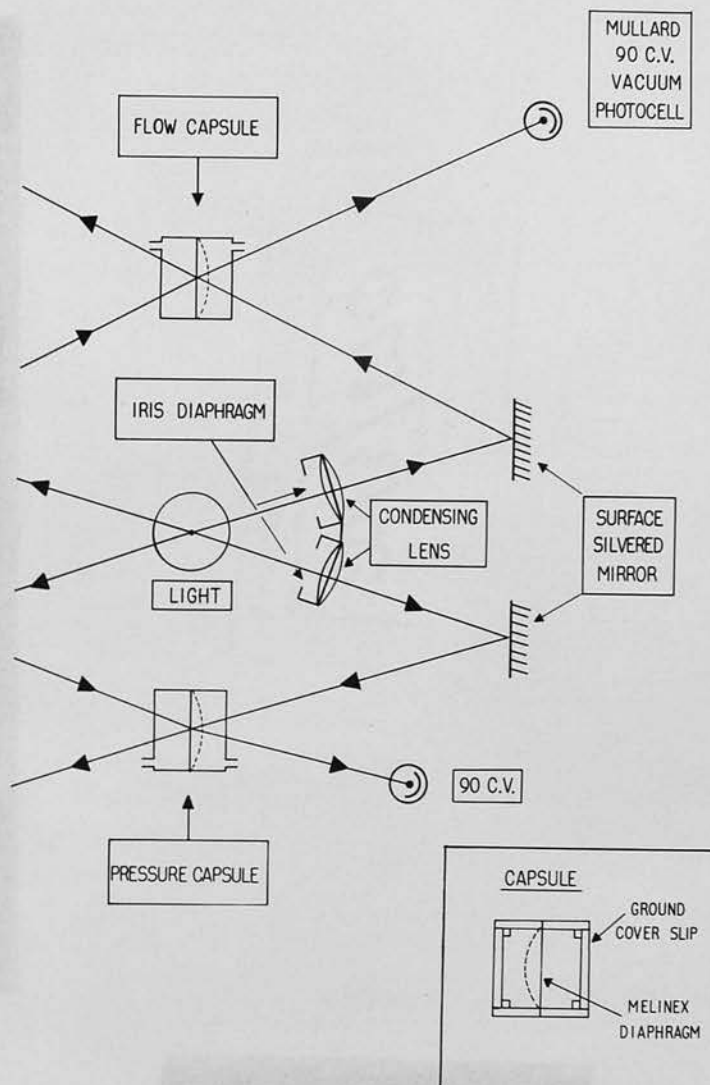
Experimental procedure for the main experiments. The inspired  $PO_2$  and  $PCO_2$  and the time of measurement of arterial  $PO_2$ ,  $PCO_2$  and pH, and of ventilation, are shown.

pneumotachygraph had one other advantage, for by this means an open circuit system could be adopted which would allow rapid changes in the inspired gas concentrations to be made. This facility was highly desirable in this study, for in the attempt to measure the "isoxic" respiratory responses to carbon dioxide inhalation, rapid adjustments in oxygen concentration of the inspired gas are essential, in order to try and achieve constant arterial  $PO_2$  values at various  $PCO_2$  levels.

The pneumotachygraph and associated manometer and electrical circuits were constructed in the Department of Medicine, University of Edinburgh. The pneumotachygraph was a modification of the Lilly (1950) design. It consists of a wire screen resistance to air flow (400 wires to the inch, in stainless steel) with a circumferential lateral pressure tap on each side of the screen. The modification from Lilly's design is to reduce the overall diameter of the airway to one inch, to reduce the dead space. The small pressure differential was transduced by a modified Greer (1958) manometer (Figure 10).

The manometer is based upon the ingenious use of the "defocussing" principle - the "Melinex" (I.C.I. Limited) diaphragm consists of an aluminised plastic sheet, of 0.00035 inches in thickness, which is stretched between the two identical halves of the cylindrical capsule. The two halves are rendered airtight by two high quality coverslips, ground to fit. The differential pressure to be measured is then led to either side of the capsule by narrow bore stiff-walled nylon tubing, which is air filled. The

# MODIFIED GREER MANOMETER : OPTICAL SYSTEM



**Figure 10**

The modified Greer manometer. The figure shows only one half of the optical layout, the other half being a mirror image of that shown.

development of a pressure differential between the two halves of the capsule results in deformation of the diaphragm, which forms a convex mirror on one side, and a concave mirror on the other. This results in the focussing of a beam of light on one side and defocussing on the other. The resultant differences in light intensity at a suitable distance from the screen can be detected by photo-electrical devices, and the electrical signal is then available for amplification and recording.

The development of this instrument posed various problems. The first instrument used was very prone to a linearity and baseline drift, which was a very serious fault if the signal was to be integrated electrically. This fault largely arose from the use of phototransistors as the photo-electric devices (Mullard OCP 71), which were very temperature dependent in their characteristics. Trials of cadmium photocells which, although stable, were very slow, led finally to the adoption of Mullard 90 CV photocells which required subsequent amplification of the signal with a balanced cathode follower amplifier. The sensitivity of the instrument was increased by lengthening the light path between the mirror and the photocells, and by using very thin Melinex to construct the diaphragm. Stability was improved by stabilising the power supply to the lamp, and temperature equilibration by running the lamp continuously.

The integration of the flow signal thus derived was carried out by a conventional resistance capacitance network, using a Solartron A.1023 type chopper stabilised operational amplifier, fed by two stabilised power supplies, the integrating capacitor being of high quality polystyrene type.



### 3. Calibration of the Pneumotachygraph and Integrator:

The linearity of the pneumotachygraph and Greer Manometer, as a flow measuring device, was established by passing gas flows at various measured rates on a rotameter, through the pneumotachygraph and measuring the resultant voltage produced from the Greer Manometer, after the cathode follower amplification stages. The results are shown in Figure 11.

It is seen that the response is linear over the range 0-70 litres/minute, for flows in either direction, and that the instrument is symmetrical, giving equal and opposite deflections for equal flows in opposing directions. In addition, the characteristics are not changed by using oxygen in place of air as a calibrating gas. This result possibly arises from the fact that both the pneumotachygraph and the rotameter are dependent on the viscosity and density of the gas, and thus both instruments will be affected equally by a change in these values.

The definitive calibration of the device as an instrument for determining tidal volume was carried out by use of the experimental procedure illustrated in Figure 12. The subject inspired and expired through the pneumotachygraph, held to the face by an Aviator's oro-nasal mask (modified Air-Med pilot's mask and head harness). In series with the pneumotachygraph was the respiratory valve (a valve incorporating the best features of the very low resistance type 1 valve of Bannister and Cormack (1954) and the low dead space value of Cunningham, Johnson and

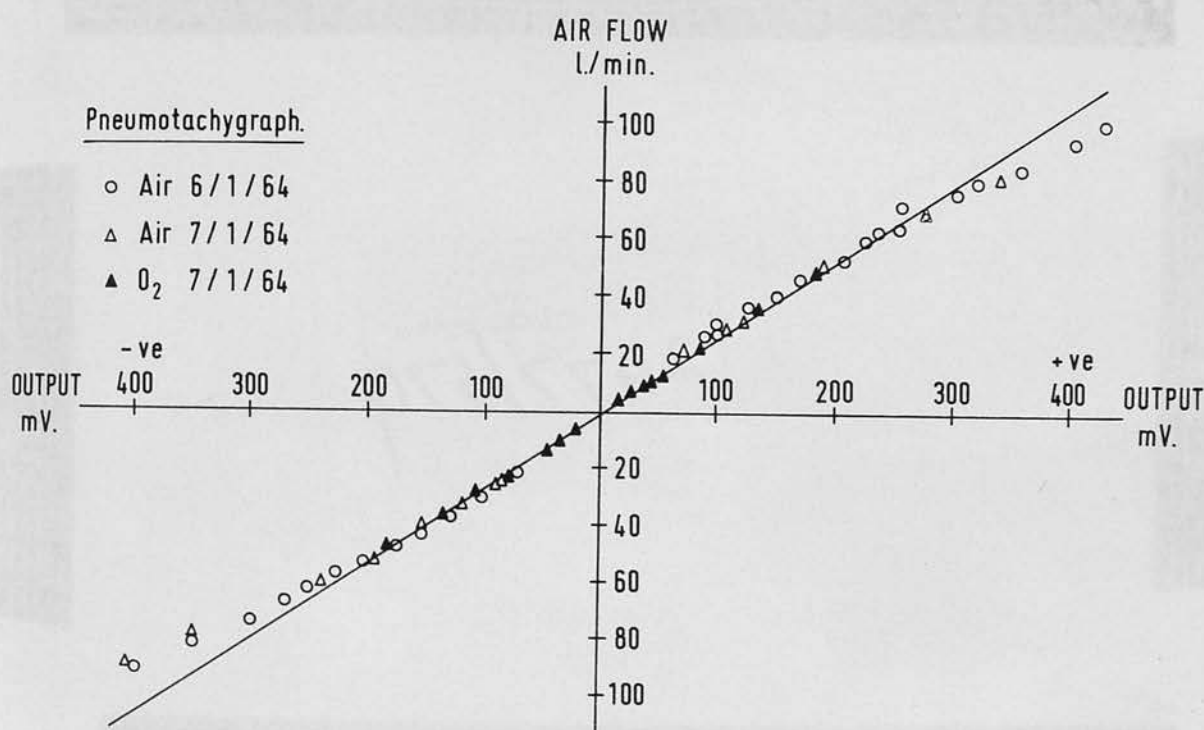


Figure 11

The results of the calibration of the pneumotachygraph and Greer manometer (flow) against flow of air and oxygen. The line is drawn by eye.

Figure 12

The experimental arrangements for calibration of the pneumotachygraph, Greer manometer and integrator system when used to measure minute volume of ventilation.

### CALIBRATION OF VOLUME MEASUREMENTS

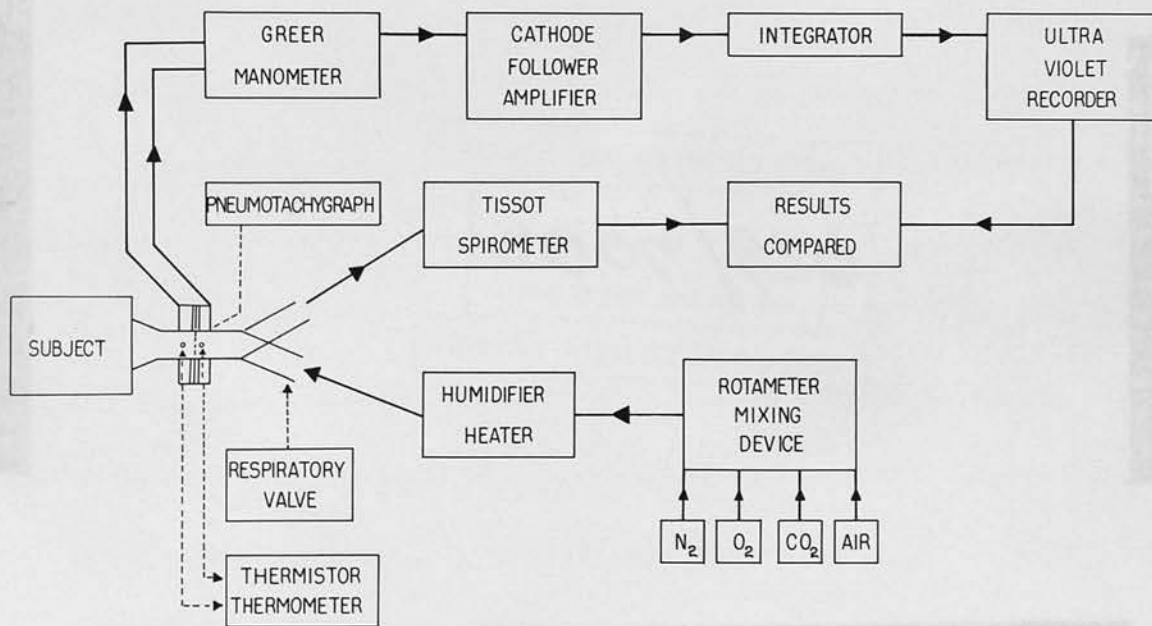


Figure 12

The experimental arrangements for calibration of the pneumotachygraph, Greer manometer and integrator system when used to measure minute volume of ventilation.

Lloyd (1956)) which ensured that the subject inspired from the warmed and humidified gas mixtures from the rotameter mixing device, and exhaled into the Tissot spirometer. The minute volume of ventilation varied from 5.0 litres/minute (BTPS) to 5.5 litres/minute (BTPS) as measured by the Tissot spirometer, this variation being produced by adding carbon dioxide to the inspired gas, which otherwise consisted of air, in the main series of calibration experiments. The integrated volume output, consisting of a roughly sinusoidal waveform, as both inspiratory and expiratory excursions were obtained, was displayed on the Ultra-violet recorder. Great care was taken to synchronise the Tissot record and the Ultra-violet record. At low minute volumes the recordings ran for three minutes, at very high minute volumes for one minute only. The total expiratory excursions on the Ultra-violet trace were measured by hand, with a ruler. These figures were converted into values of minute volume by substituting a Starling Large Animal Respirator (C.F. Palmer Ltd.) in place of the patient. This pump was set to deliver a sinusoidal stroke volume of 500 mls/minute, at 15 cycles/minute, and the deflections produced by this pump were recorded. The temperature at the pneumotachygraph screen was measured by a thermistor thermometer consisting of two Galton thermistor beads, on either side of the pneumotachygraph screen. In all the calibration experiments the inspired gas was heated and humidified (by passage through a Marshall and Spalding non-blower humidifier) in exactly the same fashion as that during the main experiments.



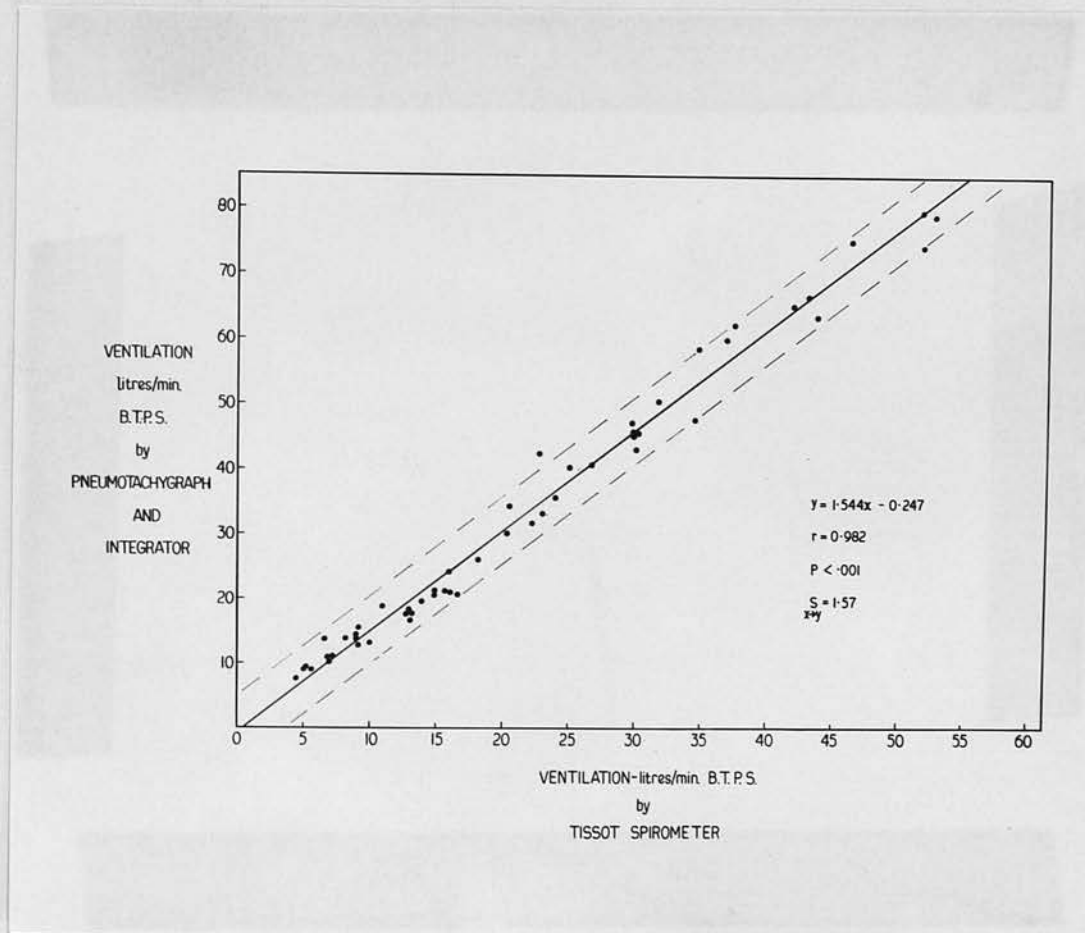
The summed expiratory excursions from the Ultra-violet record were converted into minute volume readings (litres/minute BTPS) by reference to the "calibrating" deflections of the Starling Large Animal Respirator, on the basis that this stroke volume was indeed 500 mls/minute. The Tissot spirometer record was converted into minute volume of respiration (litres/minute BTPS) by reference to the temperature of the bell, and the calibration factor relating chart reading to volume, which was obtained by accurate calibration with water displacement.

The relationship between these two simultaneous values of minute volume, obtained by the Tissot spirometer and the pneumotachygraph and integrator, is shown in Figure 13. The equation:

$$y = 1.544 x - 0.247$$

describes the relationship (where  $y$  = minute volume measured by pneumotachygraph and integrator and  $x$  = minute volume by Tissot spirometer), with a correlation coefficient of 0.982, a highly significant value ( $P < 0.001$ ) and one standard deviation about the regression line of 1.57 litres/min., for 50 determinations. In addition, ten comparisons were made when the inspired carbon dioxide mixture was given in 11% oxygen and ten comparisons when the inspired gas contained 78% oxygen, without producing a significantly different regression equation.

It is most important that this method of recording tidal volume must not produce a phase lag in the record. This point was examined by arranging that the crank of the Starling Large Animal Respirator (which delivered an



**Figure 13**

The results of the calibration of the pneumotachygraph and integrator when used to measure the minute volume against simultaneous measurements of minute volume by the Tissot spirometer.

approximately sinusoidal air flow when the valves were removed and the connections rearranged), activated a microswitch at the point of top dead centre. An electrical circuit was thereby closed temporarily, and this was arranged to produce an interference pattern on the oscilloscope record of the integrator output, displayed as a function of time. The result is shown in Figure 14. It therefore appears that phase lag was not an important fault in this system.

Despite strenuous efforts to overcome this problem, the integrated output from the pneumotachygraph did show a tendency to drift with time. This property is, of course, inherent in all integrator circuits, for any slight degree of imbalance in the input to the integrator will, needless to say, be integrated with respect to time, resulting in an electronic drift. The rate of drift of the present instrument was tolerable over a period of five minutes, following a rigid procedure of optical and electrical balancing of the Greer Manometer, with the pressure inputs connected together. Due to the presence of this drift it was not possible to use the instrument to detect long-term changes in the end tidal point. In retrospect this was the most serious deficiency of this system, but the implications of this deficiency, from the point of view of measurement of the total inspiratory work, were not apparent until after the experimental part of this study was completed (see Chapter VII). The calibration procedure of the volume recording system has been given in detail, as this is an unconventional method of recording volume, which requires careful calibration if the results obtained are to be reliable.

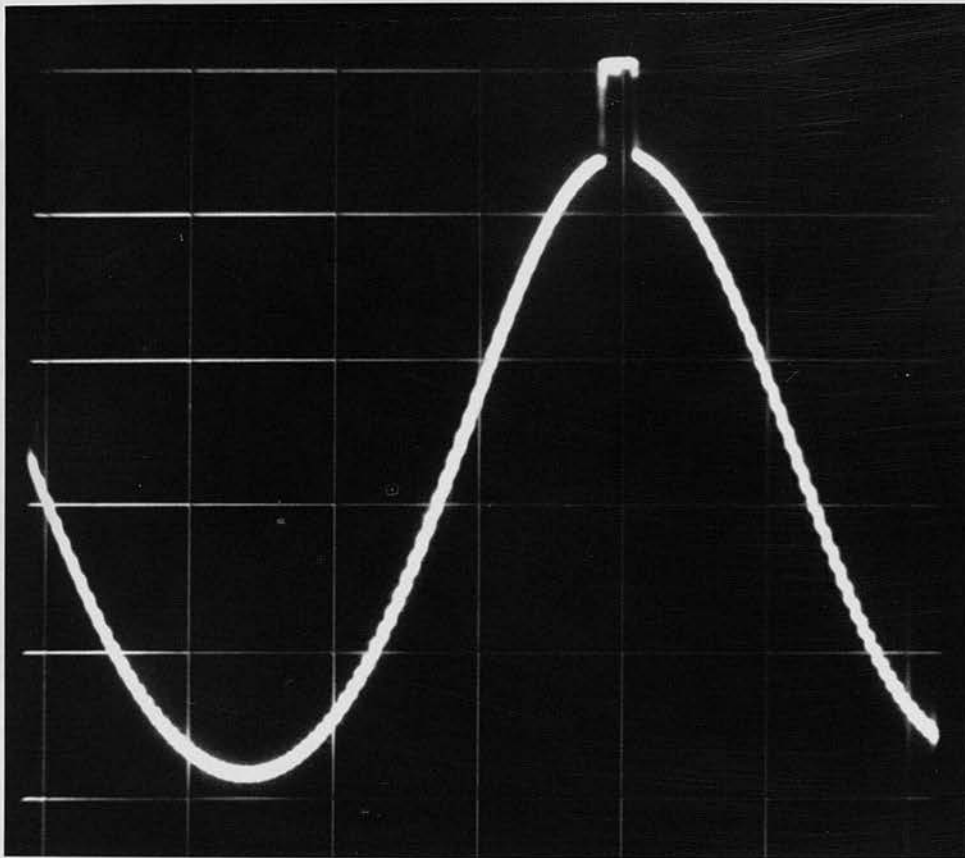


Figure 14

The output of the integrator to a sinusoidal airflow passing through the pneumotachygraph, from a Starling respiration pump. At top dead centre of the pump stroke, a micro-switch was activated producing the interference pattern on the trace. An oscilloscope camera photograph.

The pressure from the balloon was transmitted by another modified Green photo-electric manometer, which was constructed in the same instrument as that used for the pneumotachygraph (Figure 10). This pressure manometer, again a differential instrument, measured the differential pressure between the oesophageal balloon and the mouthpiece.



#### 4. The Measurement of Endoesophageal Pressure:

The endoesophageal pressure was measured by means of an air-filled balloon which was introduced into the lower third of the oesophagus. The balloon was passed through the nose, after use of an Amethocaine anaesthetic spray, and the balloon and connecting catheter were well lubricated with Xylocaine Oral Liquid (Xylocaine in a raspberry flavoured base). As the balloon was to remain in place for two to three hours, during considerable hyperventilation, attention to these details was most important. The balloon was 13 cm. long and 4.6 cm. in perimeter, and was sealed over the end of a 1 mm. bore soft polythene cannula, which was stiffened for insertion by a nylon covered "Seldinger" wire, which was then removed, leaving the soft flexible oesophageal tube in place. The end of this tube, covered by the balloon, was perforated with 8 - 12 spirally arranged holes. The potency of the tube was ensured by flushing the system with 2 mls. air, after it was in position, and then approximately 1.5 mls. of air were withdrawn, and the polythene tube connected to the recording system. This system was calibrated at the end of each period on one particular gas mixture, by reference to a water manometer, a standard calibration pressure of 10 cm. water being used.

The pressure from the balloon was transduced by another modified Greer photo-electric manometer, which was constructed in the same instrument as that used for the pneumotachygraph (Figure 10). This pressure manometer, again a differential instrument, measured the differential pressure between the oesophageal balloon and the mouthpiece.

The Greer manometer on this system was constructed so as to sacrifice sensitivity in order to obtain linearity over the range  $\pm 30$  cm. water. This was achieved by using a thicker Melinex (I.C.I. Limited) aluminised diaphragm, and by using a shorter light path from the diaphragm to the photocells.

The frequency response of the manometer was determined by creating a constant amplitude sinusoidal waveform from an electrical calibration pump. This pressure waveform, in the air-filled system, was led to one side of the pressure manometer capsule, the other being open to air. The resultant manometer output, as the frequency of the oscillation was increased, is shown in Figure 15, an oscilloscope photograph, as amplitude against time. Five per cent variation from the original amplitude occurred at a frequency of 1 cycle/second. Although this response was by no means ideal, it would appear adequate to record respiratory events at frequencies which very rarely exceeded 30 breaths/minute.

The oesophageal balloon was passed with the aid of small sips of water taken through a straw until the tip was some 50 cms. from the anterior nares. The tube was then connected to the water manometer, and the subject asked to take a deep breath. If the pressure became positive on inspiration, this indicated that the major part of the balloon was in the stomach, and the tube was slowly withdrawn until the pressure moved negative on inspiration. One to two centimetres more were then withdrawn, it being confirmed that the pressure was still negative on inspiration. The tube was then lightly taped to the patient's cheek. The position of the

bellows, after this procedure, was checked at the end of the experiments, in some subjects. In one such check, shown in Figure 16, a semilateral X-ray was taken after 5 cc. of H<sub>2</sub>O had been injected down the

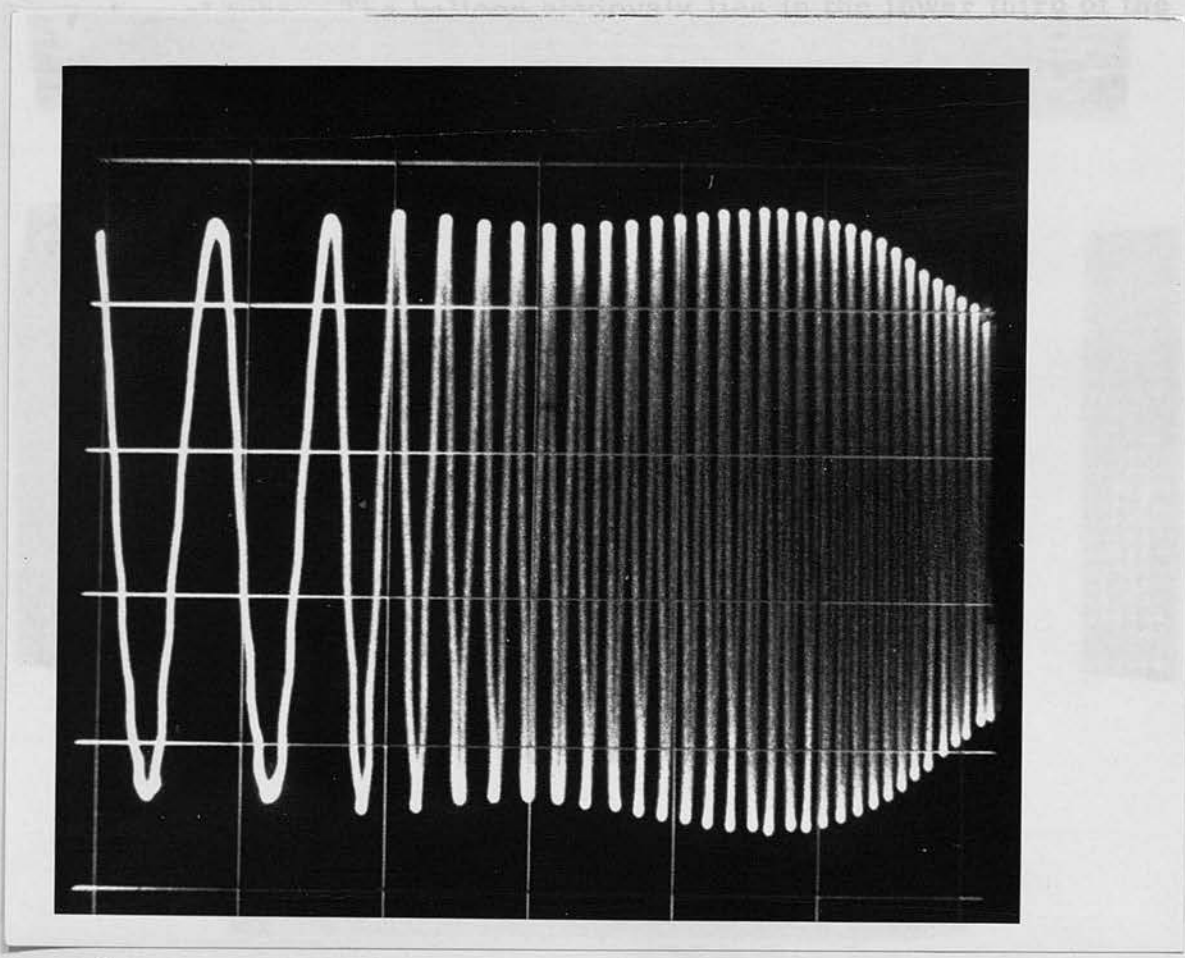


Figure 15

The output of the "pressure" channel of the Greer manometer, to a constant amplitude sinusoidal pressure pulse of increasing frequency. Five per cent variation from the original amplitude occurs at 1 cycle/second.

The reversed view of the display is shown in Figure 17.

balloon, after this procedure, was checked at the end of the experiments, in some subjects. In one such check, shown in Figure 16, a semilateral X-ray was taken after 5 ccs. of lipiodol had been injected down the oesophageal tube. The balloon obviously lies in the lower third of the oesophagus, as intended.

5. The Measurement of the Inspiratory Work Done on the Lungs:

The previous two sections have explained how the electrical analogue signals representing the tidal volume and the differential pressure between the oesophagus and the mouth were obtained. It is vital to stress that these electrical signals were continuously variable, and in phase, so that at any instant in time the size of the signals represented the values of volume and pressure at that time. The signals could therefore be displayed against each other, so that volume was displayed as a continuously variable function of the pressure differential. This was achieved by delivering the two signals to the X and Y amplifiers of an oscilloscope (Telequipment Ltd., Model D31). The display was arranged so that the vertical axis (X amplifier) after the time base was disconnected, represented pressure. The amplitude and position of the two signals could be independently varied by the gain and shift controls of the X and Y amplifiers. To obtain a time signal on this two-dimensional plot, it was arranged so that the beam brightness was interrupted five times per second, this signal (Z modulation) being derived from an independent timer unit. The resultant form of the display is shown in Figure 17.





Figure 16

X-ray photograph of an oesophageal balloon, filled with lipiodol to show the position of the balloon during an experiment. The tip of the balloon lies just above the cardia.

Dynamic pressure-volume diagram of the lungs. An experimental record, from an oesophageal catheter, showing the relationship between tidal volume on the Y axis and pressure on the X axis. The lungs are inflated by the tidal volume.

In order to record this display, an oscillograph camera (D. and S. Shackman Ltd.) was used, with a numbering device. The camera photographed the oscilloscope tube on 35 mm. Ilford 500 Oscilloscope

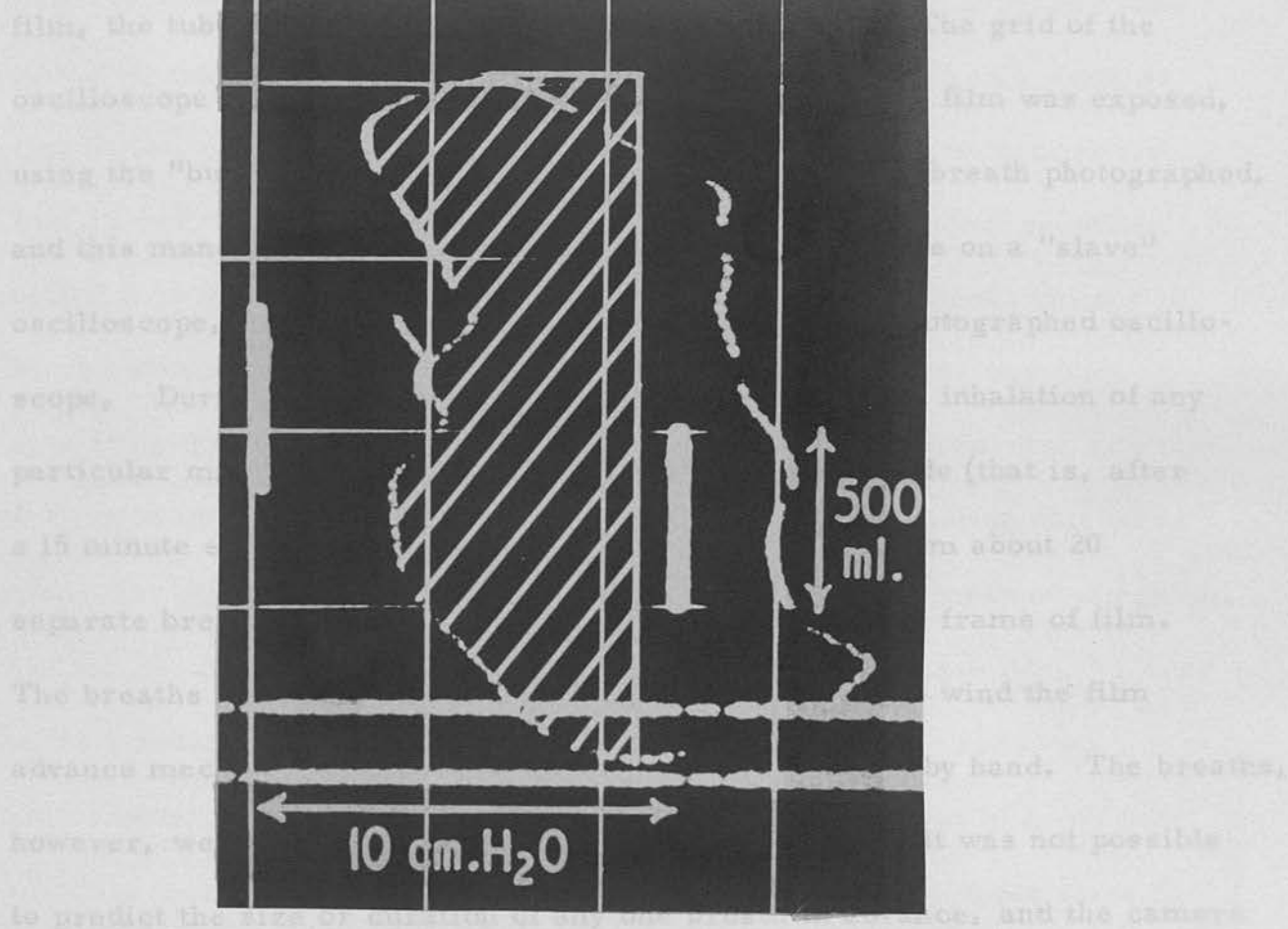


Figure 17

Dynamic pressure volume diagram of the lungs. An experimental record, from an oscilloscope camera photograph of a respiratory loop, with tidal volume on the Y axis and oesophageal to mouth pressure differential on the X axis. The loop is interrupted five times per second.

In order to record this display, an oscillograph camera (D. and S. Shackman Ltd.) was used, with a numbering device. The camera photographed the oscilloscope tube on 35 mm. Ilford 5G91 Oscilloscope film, the tube being covered by a Wratten blue filter. The grid of the oscilloscope face was illuminated by side lighting. One film was exposed, using the "bulb" setting of the camera shutter, for each breath photographed, and this manoeuvre was controlled by observing the trace on a "slave" oscilloscope, driven by the X and Y amplifiers of the photographed oscilloscope. During the last 5 - 10 minutes of each period of inhalation of any particular mixture of oxygen, nitrogen and carbon dioxide (that is, after a 15 minute equilibration period) the traces resulting from about 20 separate breaths were photographed, each on a separate frame of film. The breaths were not consecutive, due to the inability to wind the film advance mechanism of the camera with sufficient speed by hand. The breaths, however, were not selected, for the simple reason that it was not possible to predict the size or duration of any one breath in advance, and the camera shutter had to be opened without foreknowledge of the pattern of that breath. This point is important, for the statistical treatment of the results (Chapters VII and VIII) is based on the assumption that the breaths recorded are a random sample of the "population" of breaths occurring under each particular set of conditions.

A calibration procedure for both pressure and volume signals was carried out at the end of each period of the experiment, that is after each series of 20 exposures. Without altering any of the electronic controls,

the subject was disconnected from the mask, and a to-and-fro sinusoidal gas flow, of the same "500 mls." stroke volume as used in the calibration experiments (vide supra) was passed through the pneumotachygraph. The resultant signal from the volume integrator was displayed as a vertical line on the volume axis of the oscilloscope. The pressure manometer was opened to atmosphere at this point. The film of the last recorded breath was then re-exposed, for sufficient time for the stroke volume to be registered twice. A negative pressure of 10 cm. water was then applied to the Greer manometer recording oesophageal pressure, and the deflection observed on the "slave" oscilloscope. The Starling sine wave pump was still passing a gas flow to and fro through the pneumotachygraph, and the resultant deflection was again recorded on the same film, by once again opening the camera shutter for a brief period. The resultant calibration traces are shown in Figure 17. It is important to appreciate that this method of calibration used the warmed, humidified gas stream, of the same composition as that recently inhaled by the subject during the period to which the calibration applied. By this means, errors due to variation in temperature and gas composition were thereby avoided.

The 35 mm. films, after development and fixing, required to be magnified in order that measurements could be made on them. This was carried out by the film reading desk (Figure 18) designed by the author, and constructed in the Department of Medicine, University of Edinburgh. This cabinet allowed the films to be enlarged from a 24 x 24 mm. frame to



# FILM READING DESK

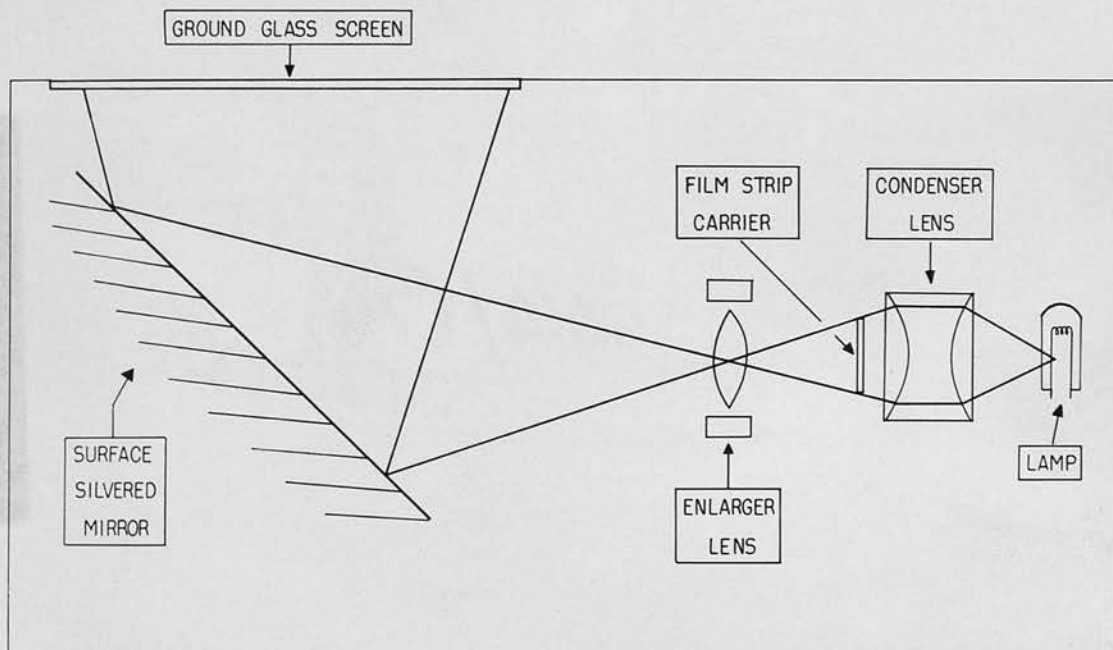


Figure 18

The optical arrangements of the film reading desk.

approximately 25 cm. x 25 cm., a linear magnification of 100 times.

As this study required measurement on some 2,500 individual frames of film, it will be apparent that the comfort of the operator, and convenience of adjustment were of some importance in obtaining accurate results.

The actual measurements made on each frame can be described by reference to Figure 19.

1. The distance V is the vertical distance between the top and bottom of the respiratory "loop". It is, of course, an expression of the tidal volume of that loop.
2. The distance A is the distance from some arbitrarily defined vertical grid mark to the lowest point of the respiratory "loop".
3. The distance B is the similar distance from the same arbitrary vertical grid mark to the highest point of the loop.
4. The area shaded //// is the area enclosed between the left-hand (or negative direction of pressure) side of the respiratory "loop" and a vertical line drawn through the lowest point of the "loop" and a horizontal line through the highest point of the loop.
5. The number of time dashes (Z modulation) marks making up the "loop".

The above measurements are made on every respiratory loop photographed except where the "loop" was technically unsatisfactory and measurements could not be made. This arose when:

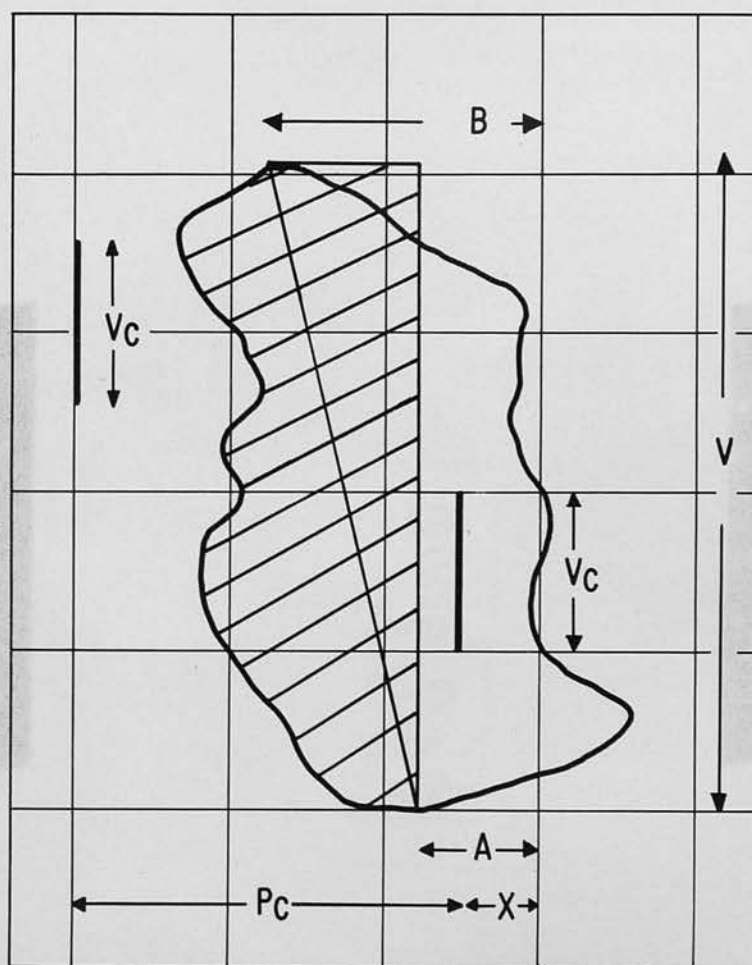


Figure 19

Dynamic pressure loop, showing the five measurements made on each loop, and the calibration measurements. For a full explanation, see text.

- a) The subject coughed, or an oesophageal contraction caused totally abnormal oesophageal pressures during a loop;
- b) A marked degree of integrator drift developed during a loop, preventing the record from "joining up" to form a loop;

It is for these reasons that it was impossible to obtain results for 20 breaths in each period on every patient, as was intended in the experimental protocol.

In addition to these measurements on every "loop", the calibration marks appeared on the last frame of each experimental period with the same inspired gas mixture. On these frames the following measurements were made:-

- 6.  $V_c$  is the length of the volume calibration signal (the same for both records).
- 7.  $P_c$  is the distance between these two volume calibration signals, produced by a known pressure differential applied to the pressure manometer.
- 8.  $X$  is the distance between the right-hand pressure calibration (at atmospheric pressure) and the arbitrarily selected vertical grid line from which the measurements A and B are taken.

#### 6. The Calculation of Tidal Volume, Minute Volume, Inspiratory Viscous Work, and Inspiratory Elastic Work per breath, and Rates of Inspiratory Viscous and Elastic Work:

The tidal volume  $V_T$  is calculated by reference to the volume calibration



thus:-

$$\text{Apparent tidal volume} = \left( \frac{V_{0.5}}{V_c} \right) F_T \text{ litres, BTPS}$$

where  $F_T$  = Temperature correction factor from the observed temperature at the pneumotachygraph screen, to values at BTPS, and 0.5 litres is the alleged stroke volume which produced the deflection  $V_c$ .

However, reference to Figure 13 shows that the minute volume, calculated from the pneumotachygraph records during the calibration experiments is in fact not equal to the minute volume of the Tissot determinations. As the timing system was not in error, it appears that this "0.5 litre" stroke volume is, in fact, in error. Applying this empirically determined calibration factor, therefore, we obtain:-

$$\text{True tidal volume} = V_T = \frac{V_{0.5}}{1.544} \frac{F_T}{V_c} \text{ litres BTPS}$$

(the non-significant intercept of the calibration equation in figure 13 is ignored in this calculation).

The Minute Volume of Ventilation is calculated by multiplying each value of  $V_T$  (as calculated above) by the respiratory frequency ( $f$ ) for that particular "loop".

If the number of 0.2 second pulses during one "loop" is  $T$ , then:

$$f = \frac{300}{T} \text{ breaths/minute.}$$

It follows that the value of minute volume ( $\dot{V}_E$ ) for that breath is:

$$\dot{V}_E = \frac{V_{0.5}}{1.544} \frac{F_T}{V_c} \frac{300}{T} \text{ litres/minute BTPS.}$$

Inspiratory Viscous Work per breath (VWT) is calculated by subtracting from the area measured that portion due to the Inspiratory

Elastic (EWT) work per breath. It is important that these values are in fact the inspiratory work done on the lung only.

Thus:

$$EWT = \left( \frac{B - A}{2} \right) \cdot \frac{10}{P_c} \cdot \frac{V_{0.5}}{1.544 V_c} \cdot \frac{F_T}{100} \text{ kilogram metres (kg.m.)}$$

Therefore, if the total area shaded = AREA, then:

$$VWT = AREA - \left( \frac{B - A}{2} \right) \cdot \frac{10}{P_c} \cdot \frac{V_{0.5}}{1.544 V_c} \cdot \frac{F_T}{100} \text{ kilogram metres (kg.m.)}$$

The corresponding values for the rate of inspiratory elastic work (REW) on the lung is:

$$REW = EWT \left( \frac{300}{T} \right) \text{ kilogram metres/minute, and the rate of inspiratory}$$

viscous work (RVW) is:

$$RVW = VWT \left( \frac{300}{T} \right) \text{ kilogram metres/minute.}$$

As for the calculation of  $\dot{V}_E$ , both REW and RVW refer to rates of work measured during the particular breath under consideration.

The dynamic compliance of the lungs (CL) is calculated for each breath as:

$$CL = \frac{V_T}{(B-A)} \cdot \frac{P_c}{10} \cdot \text{litres/cm. water.}$$

All these calculations were in fact carried out for each respiratory loop analysed, in each of the 15 subjects making a total of about 2,500 values for each of the variables  $V_T$ ,  $\dot{V}_E$ , EWT, VWT, REW, RVW, and CL. This task was carried out by the Elliott 803 computer at the Scottish Medical Automation Centre, from the analysis of the problem given above, and the data presented as values of V, A, B, Area, T,  $F_T$ ,  $V_c$  and  $P_c$ . The mean values, standard deviation, maxima and minima for each experimental period for each patient were calculated by the computer.

## 7. The Measurement of the Work of Breathing of the Chest Wall:

In order to determine the work done in moving the chest wall during inspiration, it is necessary to determine the static pressure volume relationships of the chest wall. As discussed in Chapter III, this is usually done by determining the relaxation pressure volume curve of the lung (static compliance line) and thereby obtaining the relaxation pressure volume curve of the chest wall. The method of voluntary relaxation against a closed tap, at various lung volumes, was criticised in that Chapter, when applied to normal subjects. The objections to the method become even more pronounced when it is applied to bronchitic subjects. Such patients cannot, in fact, voluntarily relax their respiratory muscles, and any attempt to derive a relaxation pressure volume curve is therefore farcical.

In order to overcome this problem, an alternative method of measuring the mechanical properties of the chest wall is required. This method is based upon that described by Heaf and Prime (1956). They argued that the end tidal point always represented a point where the inspiratory and expiratory muscles were relaxed, with no nett muscular forces acting on the thoracic cage. Changes in the volume of gas within the thorax can be produced by breathing from a positive or negative pressure (with respect to atmosphere). If again, even under such conditions, the end tidal point is a point at which there are no nett muscular forces acting on the thorax, it then is possible to draw a "relaxation"

pressure volume line, by plotting the airways pressure against the lung volume at the end tidal point, during positive and negative pressure breathing. The fundamental contention of this method has been supported by Naimark and Cherniack (1960) who found that no respiratory electromyographic activity was recorded at the end tidal point in three normal subjects who were subjected to positive or negative pressure breathing in a body plethysmograph.

The method used in this investigation produced positive or negative pressure breathing by the simple expedient of putting weights either on the bell, or on the counterweight arm of a closed circuit Benedict-Roth spirometer (C. F. Palmer Limited) and recording the volume changes so produced (Figure 20). The pressure produced by a known weight was determined by calibration of the spirometer system against a water manometer. The base line of oxygen consumption rate is drawn by eye through the end expiratory points of all breaths when no pressure is applied, in the conventional manner. The amount of upward deflection from this base line is then measured at each level of applied pressure. In the example shown in Figure 20, only positive pressures were used. The mean end expiratory level of these breaths is estimated by eye, and line of equal slope to the base line is drawn through these points. The resulting table of volume displacement against pressure is then plotted as shown in Figure 21. The straight line through the origin is fitted by eye, and this is labelled the "experimental total thoracic



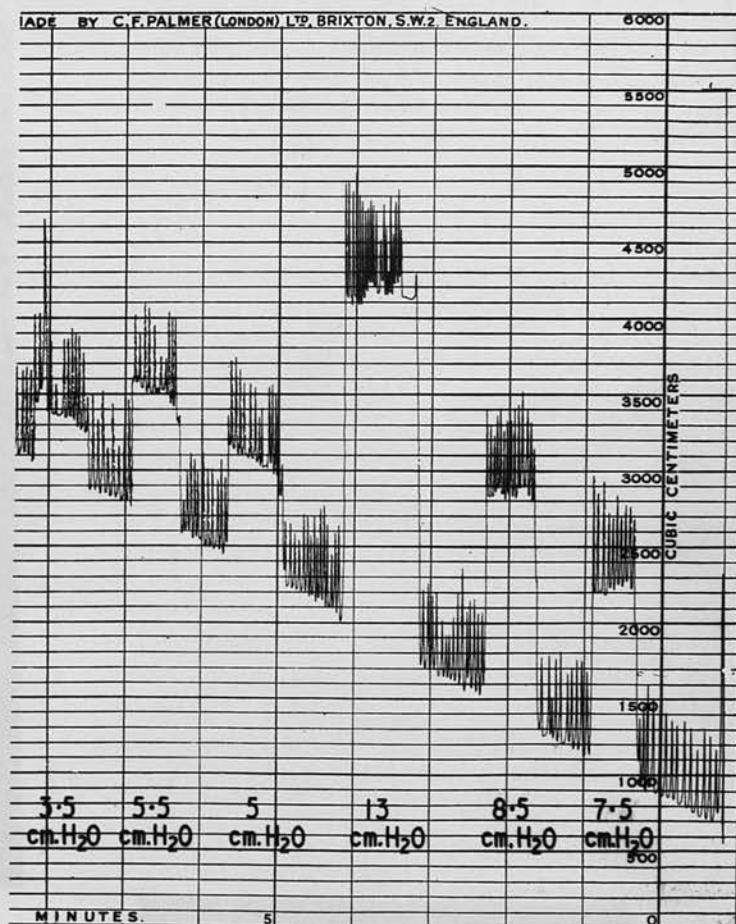


Figure 20

Experimental record of volume displacements during quiet breathing from an oxygen filled spirometer, with carbon dioxide absorption. At various times a weight, sufficient to produce the stated pressure, is applied to the spirometer bell, and later removed.

compliance line". This line must, however, be corrected for the volume changes which would occur in the spirometer alone, when the same pressure is applied. This correction yields the "corrected total thoracic compliance line". The dynamic lung compliance line is already known from the calculations of the previous section, and the chest wall

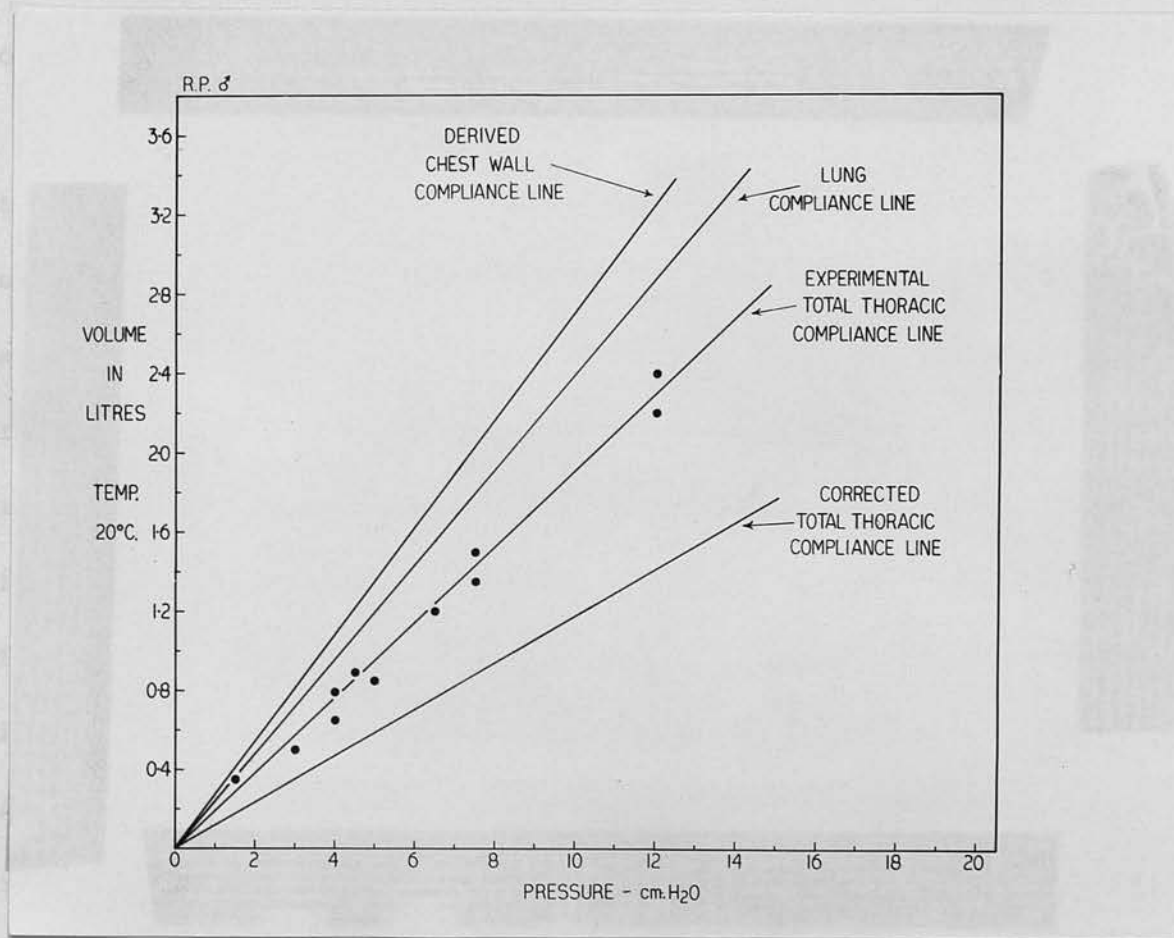


Figure 21

The method of deriving the chest wall compliance line.

differential pressures across the lungs (oesophageal to airway), and across the chest wall (oesophageal to subpleural) were measured simultaneously (Figures 22 and 23). Two separate manometers (the Statham Type P6 differential strain gauge manometer and the Statham Type P23 differential

compliance line". This line must, however, be corrected for the volume changes which would occur in the spirometer alone, when the same pressure is applied. This correction yields the "corrected total thoracic compliance line". The dynamic lung compliance line is already known from the calculations of the previous section, and the chest wall compliance is derived again by subtraction.

The above method was particularly developed in the early stages of the study, and was shown to yield repeatable results in normal subjects (Flenley, 1964), see Chapter IX. However, in the bronchitic patients the problem was far from easy. One of the major technical problems was that of providing a close seal to the face during positive or negative pressure breathing, for leaks rendered absolute measurements of volume changes totally unreliable. This was solved finally by use of Royal Air Force "Type P" and "Type Q" pressure breathing masks, kindly loaned by courtesy of Squadron Leader J. Ernsting, Institute of Aviation Medicine. Using these masks repeated series of pressure breathing measurements were made in both normal and bronchitic subjects. In two subjects (one normal and one bronchitic) full experiments were carried out to directly measure all components of the thoracic compliance during positive and negative pressure breathing. In these subjects the differential pressures across the lungs (oesophagus to airway), and across the chest wall (oesophagus to atmosphere) were measured simultaneously (Figures 22 and 23). Two separate manometers (one Statham Type P6 differential strain gauge manometer and one Greer type differential

## PRESSURE BREATHING : NORMAL SUBJECT

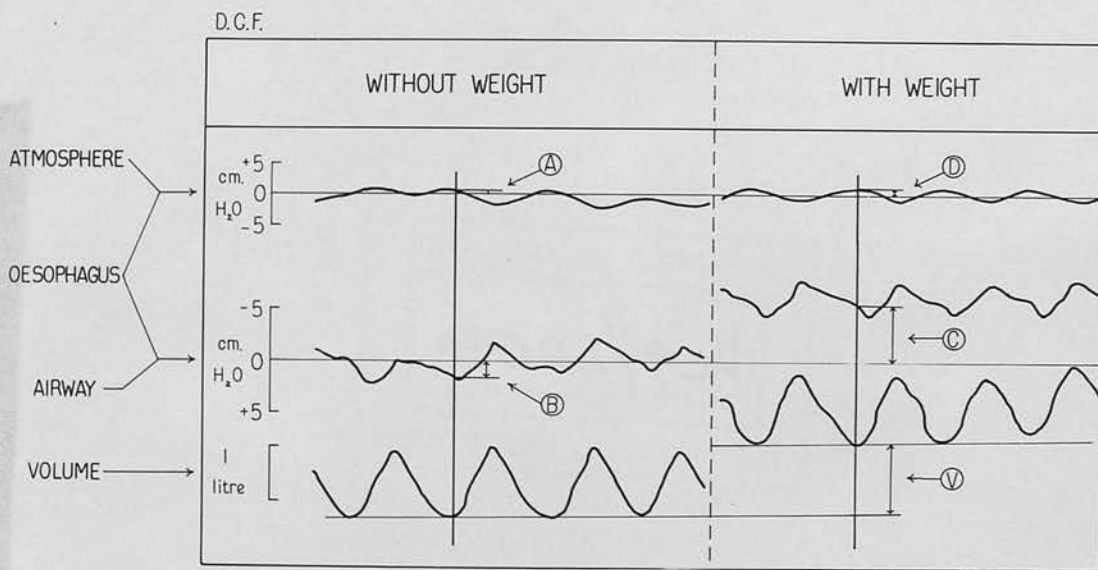


Figure 22

Traces from ultraviolet recorder of the pressure differentials between atmosphere and the airway (across the thoracic wall) and between the oesophagus and the airway (across the lung), and the tidal volume, during normal and positive pressure breathing, in the normal subject.



# PRESSURE BREATHING : BRONCHITIS

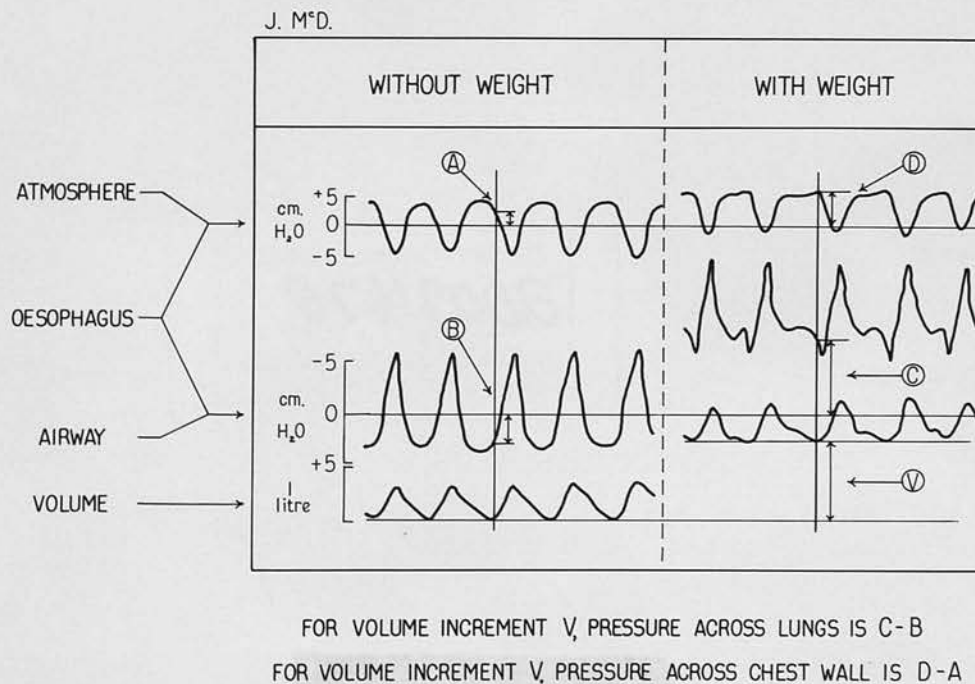


Figure 23

Traces from ultraviolet recorder of the pressure differentials between atmosphere and the airway (across the thoracic wall), and between the oesophagus and the airway (across the lung), and the tidal volume, during normal and positive pressure breathing, in the bronchitic patient.

manometer) were used, and records of the two pressures and the volume of the spirometer were recorded simultaneously on the Ultra-violet recorder during positive and negative pressure breathing. The form of records is shown in Figure 22(normal) and in Figure 23 (bronchitic). From these records the pressure volume curves of both the lungs and the chest wall were directly plotted. Regression lines were drawn through the experimental points (Figure 24, normal, and Figure 25, bronchitic). Whilst these lines are both significant for the normal subject, they are, in fact, not significant (for the chest wall) in the case of the bronchitic patient.

It would therefore appear that this method of constructing pressure volume relationships for the chest wall is, in fact, not sufficiently accurate to allow much reliance to be placed on values for chest wall work, in patients with severe bronchitis. This would probably arise from the difficulty of producing relaxation of the inspiratory and expiratory muscles at the end-tidal point during positive and negative pressure breathing in these patients. No electromyographic studies were undertaken in these patients, and therefore this point cannot be established with certainty. The alternative method of inducing anaesthesia with additional curare-like preparations does not appear ethical in these poor risk patients.

In conclusion, therefore, the present study did not solve the problem of measurement of the relaxation pressure volume properties

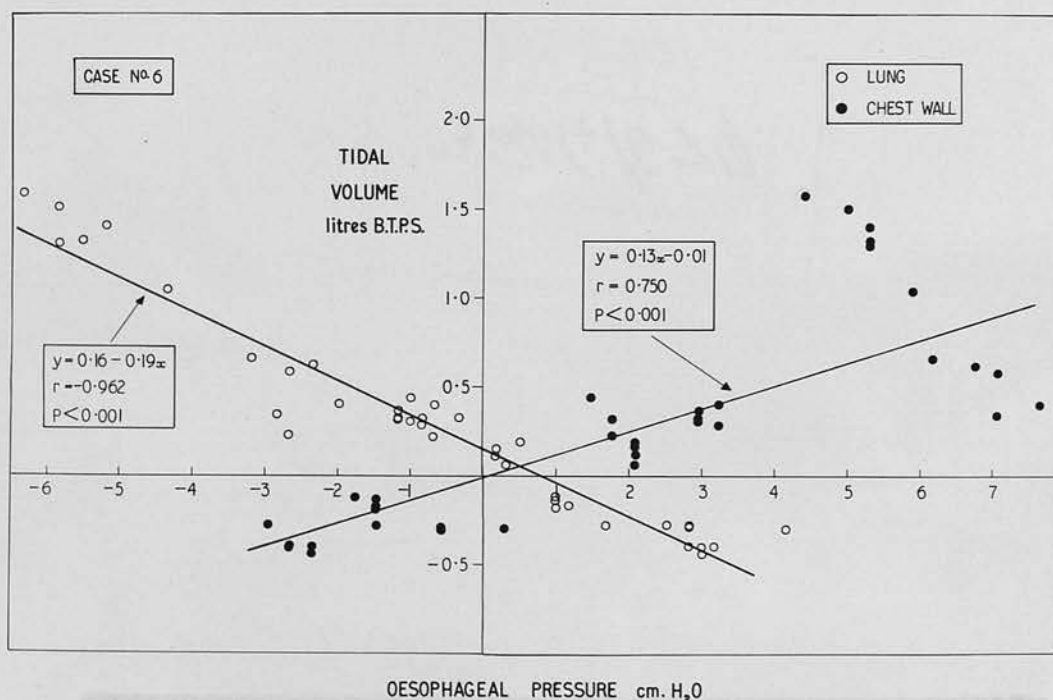


Figure 24

The experimental relationship between the differential pressure and volume, at the end tidal point, for both chest wall and the lung measured from traces of the type shown in Figure 22, for normal subjects.

The experimental relationship between the differential pressure and volume at the end tidal point, for both chest wall and the lung measured from traces of the type shown in Figure 23, for the bronchitic patients.

of the whole thorax and its components in these ill patients with ventilatory failure. As a result I am unable to present completely reliable figures for the elastic components of total inspiratory work in bronchitic patients.

### 8. Subsidiary Experiments:

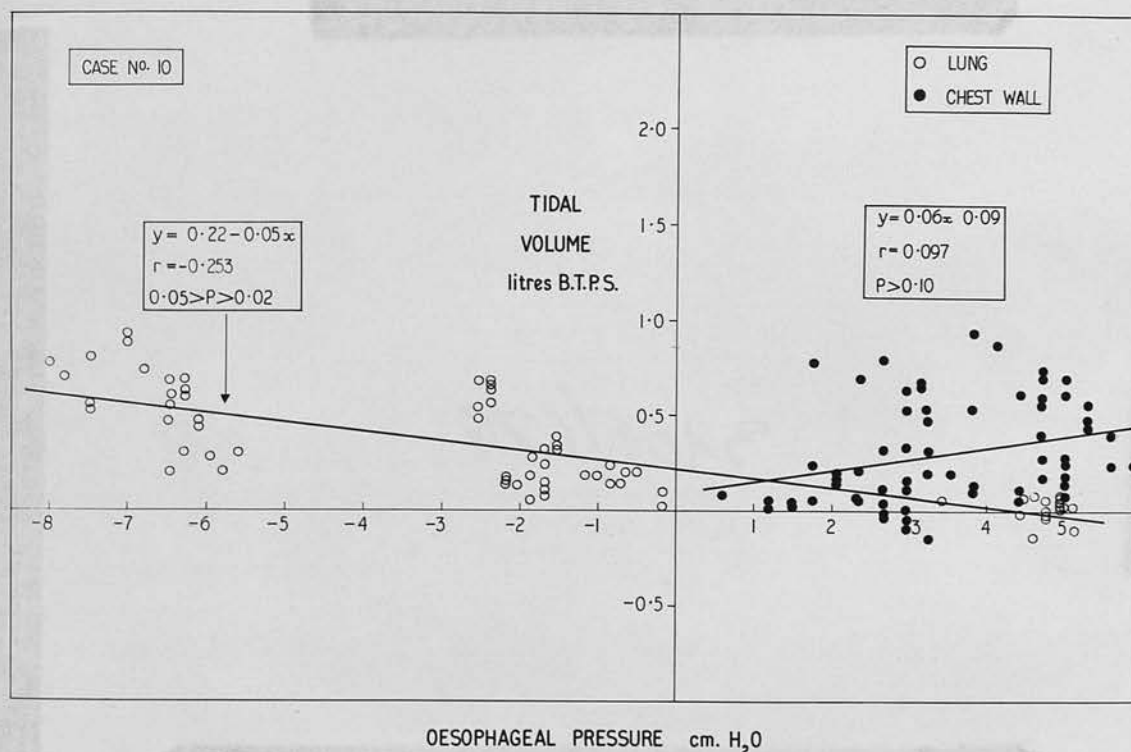


Figure 25

The experimental relationship between the differential pressure and volume at the end tidal point, for both chest wall and the lung measured from traces of the type shown in Figure 23, for the bronchitic patients.



of the whole thorax and its components in these ill patients with ventilatory failure. As a result I am unable to present completely reliable figures for the elastic components of total inspiratory work in bronchitic patients.

#### 8. Subsidiary Experiments:

After completion of the main series of experiments involving measurements of ventilation and work of breathing in normal subjects and bronchitic patients, it became apparent that analysis of the effects of hypoxia on the ventilatory response to carbon dioxide were prejudiced by failure to maintain "isoxic" conditions on the low  $PO_2$  ventilation/carbon dioxide lines. The subsidiary experiments were designed to remedy this defect, and measurements of ventilation alone were made at various levels of arterial  $PO_2$ ,  $PCO_2$  and  $(H^+)$  concentration. A similar experimental protocol, with 15 minute periods of three to four hypoxic periods at increasing  $PCO_2$  levels, followed by four periods with decreasing  $PCO_2$  levels, yet at high oxygen levels, was used. A typical protocol is shown in Figure 26. In these experiments therefore, the inspired carbon dioxide changed only slightly between each period, but the inspired oxygen changed suddenly from low levels (intended to keep a constant arterial  $PO_2$ ) to high levels of  $PO_2$  in the middle of the experiment.

In these experiments, carried out on ten bronchitic patients (see Chapter VII for details of patients), ventilation was measured by conventional means, using the respiratory valve mentioned earlier, and

a Tissot spirometer. The humidified inspired gas mixtures in these experiments were delivered from the rotameter system.

In order to provide a mean atmospheric pressure at the respiratory valve, a further vacuum cleaner, working as a suction pump,

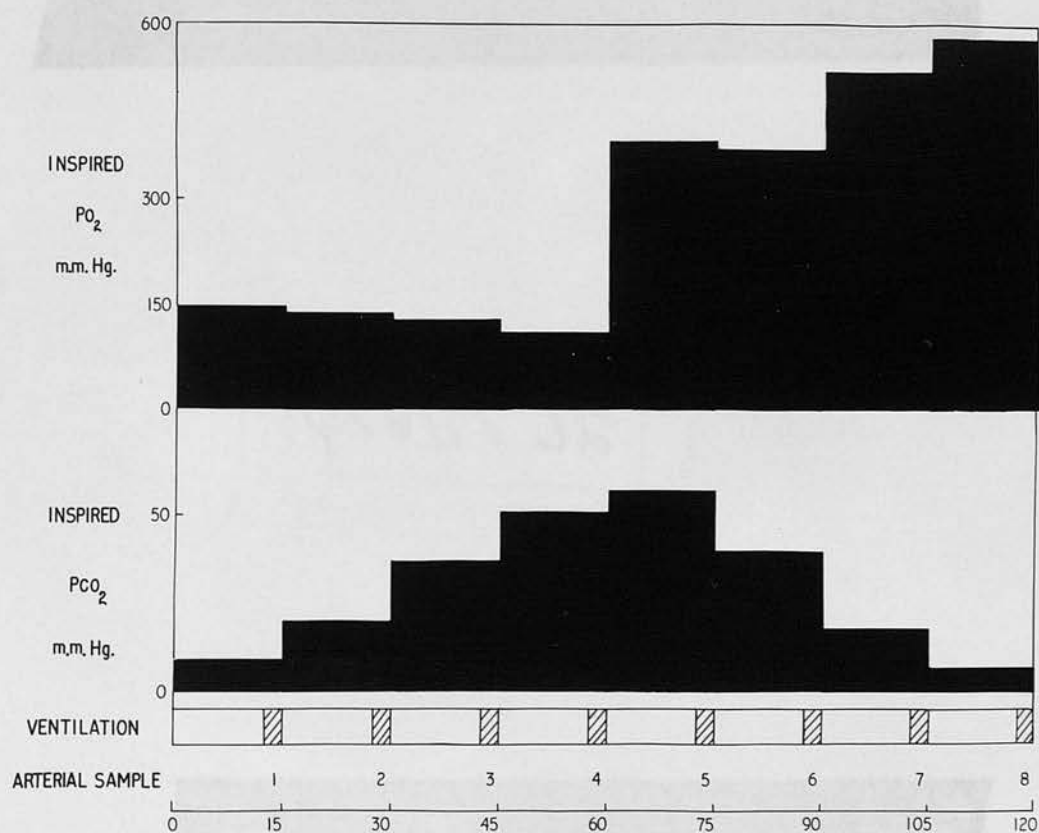


Figure 26

The experimental procedure for the subsidiary experiments. The inspired  $PO_2$ , and  $PCO_2$  and the time of measurement of arterial  $PO_2$ ,  $PCO_2$  and pH, and of ventilation, are shown.

a Tissot spirometer. The humidified inspired gas mixtures in these experiments were delivered from the rotameter system.

In order to provide a mean atmospheric pressure at the inspiratory valve, a further vacuum cleaner, working as a suction pump, was incorporated in the system, downstream from the inspiratory valve. By adjustment of the rates of flow of the vacuum cleaner (operating as a blower) supplying air to the rotameter mixing system, and this downstream vacuum cleaner (operating in suction), it was possible to arrange that the pressure at the inspiratory valve was maintained slightly below atmospheric (1 - 2 cm.  $H_2O$ ). This was found to be desirable to keep the inspiratory valve shut, yet imposed the minimum of inspiratory resistance on the patient. The total gas flow in the system was of the order of 100 litres/minute.

Again in these experiments, trial arterial  $PO_2$  measurements were made after five minutes of breathing any particular mixture, and, from the experience of the main experiments, aided by this improved gas delivery system, control of the arterial  $PO_2$  on an isoxic line was more nearly achieved.

## CHAPTER VI

### THE MEASUREMENT OF BLOOD GAS TENSIONS

#### AND pH



## CHAPTER VI

### THE MEASUREMENT OF BLOOD GAS TENSIONS AND pH

In 1896, Haldane and Lorrain-Smith published a paper in the Journal of Physiology in which they concluded that the normal arterial oxygen tension ( $PO_2$ ) was 200 mm.Hg as measured by their carbon monoxide method. As shown in Chapter III, this was in fact approximately twice the value which is now accepted. If, therefore, such a great experimental physiologist as J. S. Haldane could be so completely wrong, it is perhaps behoves lesser mortals to tread warily in this difficult field. The work described in this thesis depends so much upon the accurate measurement of arterial blood gas tension, that it appeared essential to investigate this matter in some detail, and indeed a considerable amount of work has been done on this topic. It therefore appears important to devote a chapter to the matter.

In order to assess the accuracy of measurements of  $PCO_2$  and  $PO_2$  in blood, it is necessary to produce blood samples of known  $PCO_2$  and  $PO_2$  and to determine the accuracy with which these known values are reproduced by the measuring system.

#### 1. The Electrodes:

In this work the measuring systems used were the commercial electrodes, manufactured by the Radiometer Co. Ltd. (Copenhagen); the type E5044/D615  $PO_2$  electrode and the type E5030/D619  $PCO_2$  electrode.

The oxygen electrode is of the Clark cell type consisting of a platinum cathode (diameter  $20\mu$ ) with a silver/silver chloride anode, the electrolyte being a buffered phosphate solution containing potassium chloride. The electrolyte and cathode are separated from the blood sample by a  $20\mu$  polypropylene membrane. The electrode is mounted in the stainless steel cuvette type D 615, in which the blood sample is not stirred. This electrode is therefore conventionally described as "an unstirred micro - cathode oxygen electrode". The platinum cathode is held at 700 mV negative with respect to the anode, and the current flowing between anode and cathode in this system is proportional to the oxygen tension at the cathode, which is equal to the  $PO_2$  of the sample, when diffusion of oxygen across the thin polypropylene membrane has occurred. This current is of the order of  $10^{-8}$  to  $10^{-11}$  amp. /mm. Hg  $PO_2$  and is measured by recording the voltage drop across a fixed resistor.

In the apparatus used, the commercial meter was not used, but an electronic system constructed in the Department of Medicine was used, made by Mr. J. A. Ramsay to his own design. This system uses a Vibron 33B electrometer as the null detector in a potentiometric circuit. The potentiometer is in fact formed by a Beckman Duodial precision 15 turn Helipot, capable of reading to 1 part in 1500 divisions. The polarographic potential of 700 mV is provided from a Mercury cell, as is the voltage source for the potentiometer.

The carbon dioxide electrode is a commercial development of the Severinghaus design (Severinghaus and Bradley, 1958). A glass electrode, of special design, measures the pH of a bicarbonate solution. This solution is held in the interstices of a thin layer of neutral filter paper (Joseph paper) closely applied to the glass electrode. In turn this bicarbonate solution is separated from the blood sample by a 12 $\mu$  film of "Teflon" which is permeable to carbon dioxide but not to hydrogen ions or protein. It therefore follows that the pH of the bicarbonate solution depends upon the  $PCO_2$  of the solution, which in turn is in equilibrium with the  $PCO_2$  of the blood sample. The pH of the solution is measured again on the Vibron 33B electrometer, using a "backing off" system involving a Beckman duodial precision Helipot which is shunted by resistors in parallel so that the position of the Helipot dial is related logarithmically to the resistance, and therefore to the derived potential. In this way the Helipot reading is made to be a linear function of the  $PCO_2$  of the sample.

The pH electrode used was the Radiometer G927/2, with the calomel reference electrode K497. The output of this electrode was also measured with a potentiometric circuit based on the Vibron 33B electrometer as null detector, and a Beckman precision Helipot. All the electrodes were kept at 37°C by water circulating from a Radiometer VTS13 thermostatically controlled water bath.

## 2. Tonometry:

The first experiments in calibration of the  $\text{PO}_2$  electrode were carried out by passing humidified gas mixtures, consisting of  $\text{N}_2$ , carbon dioxide and oxygen (made up in Douglas Bags using the rotameter mixing system to approximate concentrations) into a 100 ml. siliconed conical flask, containing 10 mls. of fresh heparinised blood. The flask was held horizontally in a water bath at  $37^\circ\text{C}$  and shaken at 30 oscillations per minute. Blood samples were withdrawn after 30 minutes for constant readings were obtained after this period. The effluent gas was analysed on the Lloyd-Haldane apparatus, duplicate analyses agreeing to 0.03% for carbon dioxide and oxygen. These values were then converted to gas tensions, the Barometric pressure being measured by a mercury barometer.

The results obtained in calibration of the  $\text{PO}_2$  electrode, with this tonometer are shown in Figure 27. The large random error, shown as the scatter about the regression line, was very disappointing. It appeared possible that the tonometer was not very efficient, and a new tonometer was therefore designed.

## 3. The New Tonometer (Figure 28):

This was constructed to my design by Precision Machining (Edinburgh) Ltd. It consists of a horizontal chromium plated brass cylinder, with a "perspex" lid at one end, the cylinder being placed in a water bath kept at  $37^\circ\text{C}$ . The cylinder contains a central axle, bearing nine "Perspex"



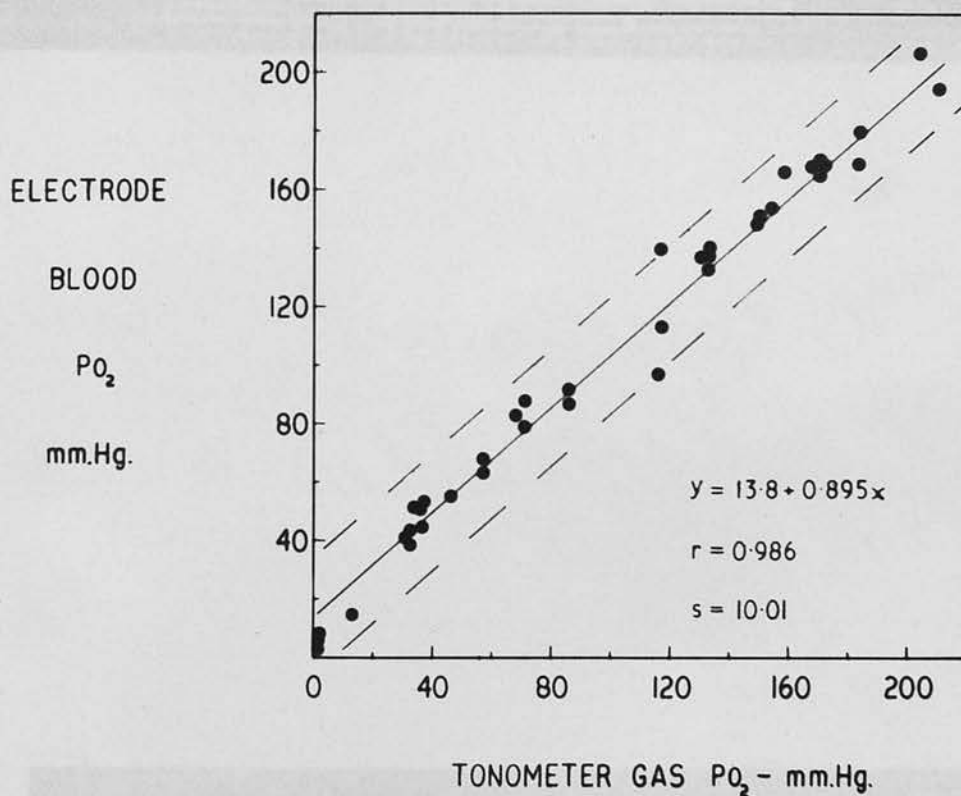


Figure 27

The calibration line of the Radiometer E5044 PO<sub>2</sub> electrode using the shaking flask tonometer. The dotted lines are at the 95% confidence limits. One reading on each sample.

# NEW TONOMETER

(EXPLODED VIEW)

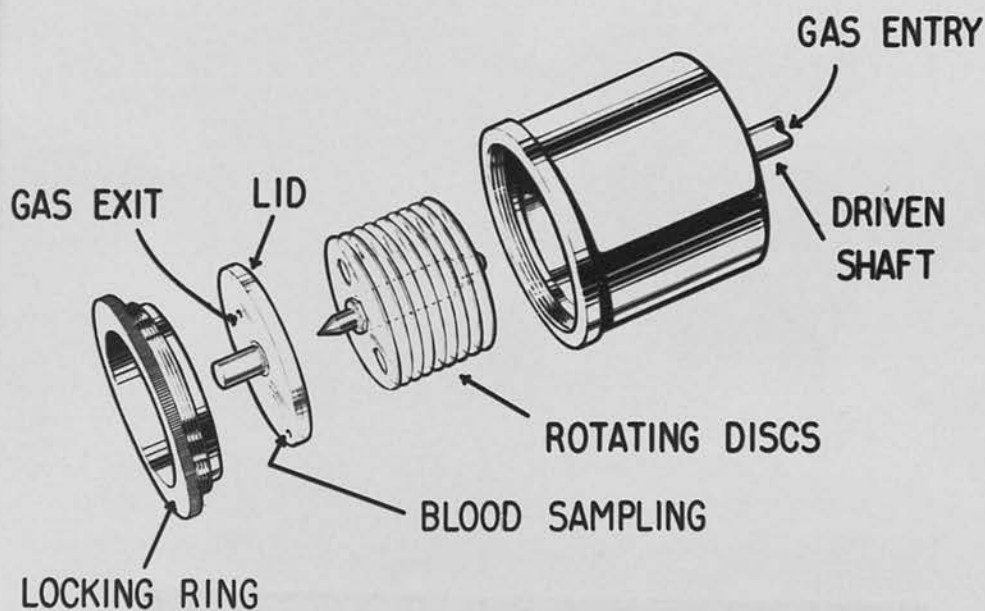


Figure 28

An "exploded" view of the new tonometer, which is placed horizontally in a thermostatted water bath.

discs, which just clear the wall of the cylinder. The axle and the discs are rotated at 15 revs./minute, by a drive carried through a gland in the water bath wall. Gas is delivered from Douglas Bags via a small diaphragm pump (Charles Austen Ltd.) at about 500 mls/min. to a sintered disc wash bottle humidifier in the water bath, and then via a water trap (in the bath), to the chamber of the tonometer. This is achieved by gas entering through a gland in the rear of the cylinder, and then through the hollow axle to the chamber, emerging through holes in the axle between the rotating discs. Gas leaves through a hole in the "Perspex" lid, and blood samples are introduced and taken from a hole in the lower end of the lid. The pressure within the tonometer, during such gas flow, is between 1 and 2 cm. water above atmospheric. All metal surfaces of the tonometer which are in contact with blood are heavily siliconed. With a charge of 20 mls. of heparinised blood the surface area available for gas exchange is approximately 180 sq.cm., as blood is carried on the rims of the discs which dip into the blood lying in the dependent segment of the horizontal cylinder. The tonometer can easily be disassembled for cleaning.

#### 4. The Performance of the New Tonometer:

This was assessed from the point of view of:-

- a) Production of haemolysis;
- b) Rate of equilibration;
- c) Calculation of diffusing capacities for oxygen and carbon

dioxide, with various volumes of blood in the tonometer.

The production of haemolysis was examined by equilibrating freshly drawn venous blood (from the author or his colleagues) for various times up to 40 minutes, and withdrawing samples at 20, 30 and 40 minutes. The plasma haemoglobin levels in these samples were determined (Shinowara, 1954) and the results shown in Figure 29. In addition, blood from a patient with a congenital haemolytic anaemia (Chromium red cell survival 14 days as opposed to a normal of 25-30 days) was also used in these experiments. The arbitrary level of 50 mg/100 ml. plasma for free haemoglobin, suggested as the acceptable level by Ravin and Briscoe (1964) was not exceeded except at 40 minutes in the patient with haemolytic anaemia. As the time period used in practice is a maximum of 20 minutes this would appear acceptable.

The rate of equilibration was studied by passing a gas mixture of  $\text{PO}_2$  183 mm.Hg into the tonometer at time 0 when the tonometer was charged with 20 mls. of freshly drawn venous blood, and samples withdrawn for  $\text{PO}_2$  estimation by the electrode at 10, 15, 20 and 25 minutes. The results are shown in Figure 30. In addition, as shown in this figure, the converse experiment was also carried out, where 100% "white spot" nitrogen was substituted for the oxygen mixture, and again samples taken for  $\text{PO}_2$  estimation at 10, 15, 20, 25 and 30 minutes. From these experiments it was concluded that 20 minutes was sufficient for full equilibration.



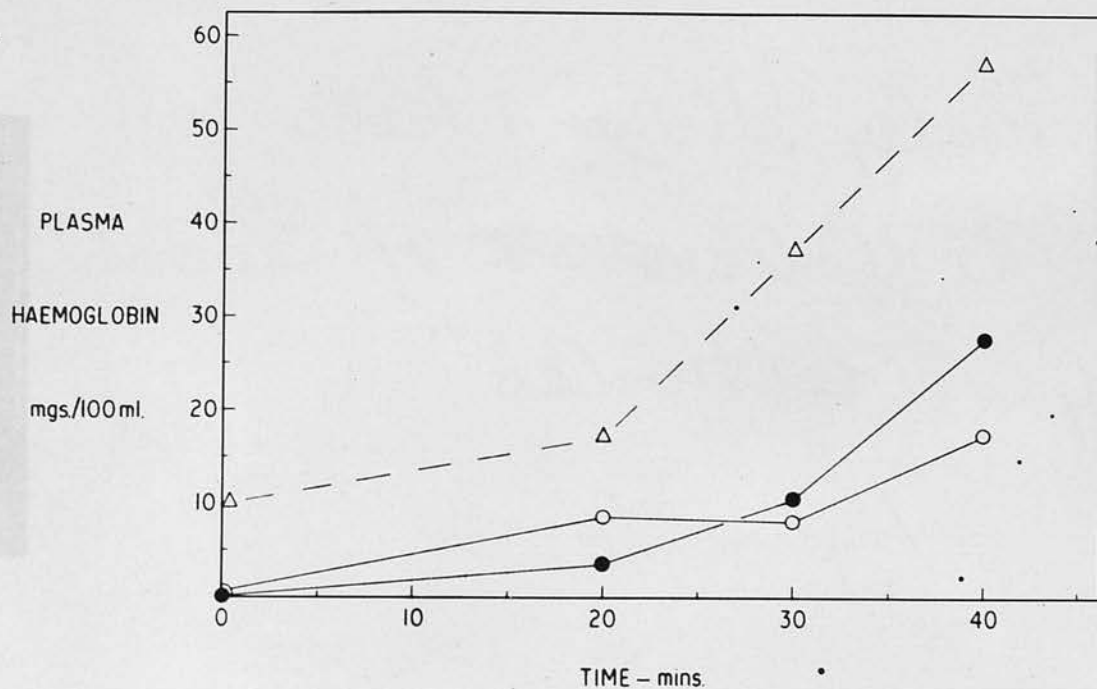
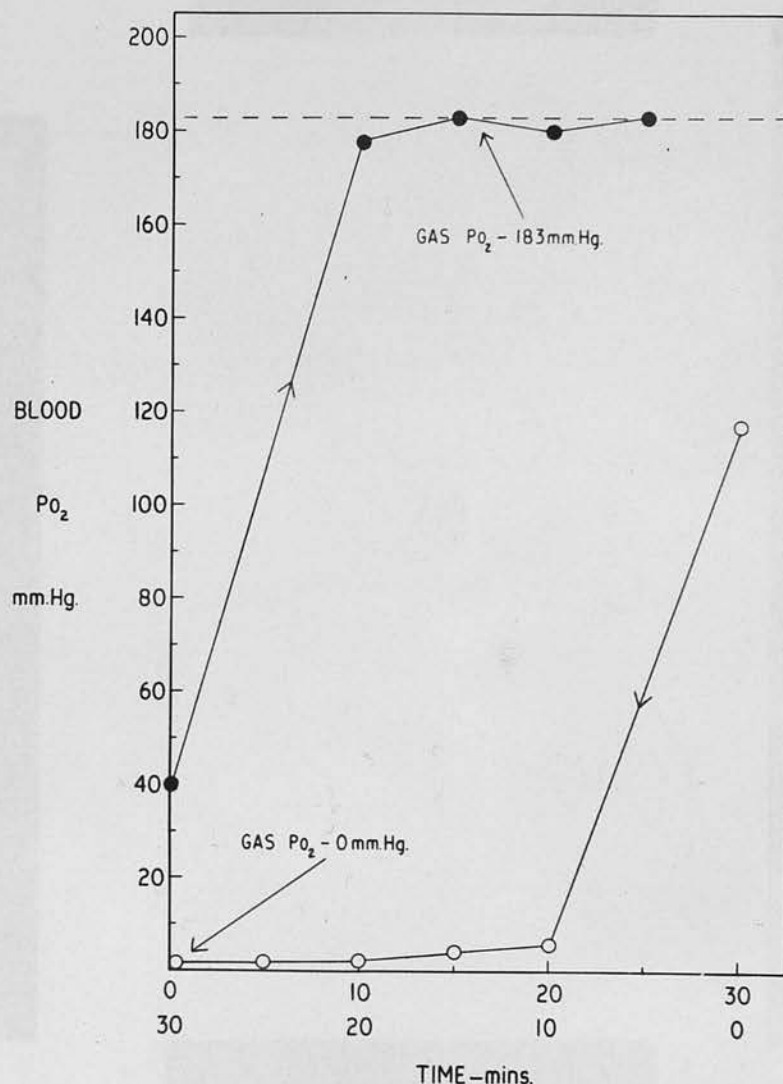


Figure 29

The production of haemolysis by the new tonometer. The continuous lines represent results on blood from two normal subjects, the dotted lines results on blood from a patient with haemolytic anaemia.



**Figure 30**

The rate of equilibration of gas and blood with the new tonometer, with regard to  $PO_2$ . The closed circles represent the  $PO_2$  in blood samples taken at the indicated times after the start of tonometry of fresh venous blood with a gas of  $PO_2$  183 mm.Hg, the open circles when white spot nitrogen was used as the tonometer gas.

The problem of the rate of equilibration in a tonometer, however, is obviously similar to equilibration occurring in the lung, and therefore the diffusing capacity for both oxygen and carbon dioxide can be studied, as Ravin and Briscoe (1964) suggest. This was done in the present study. The diffusing capacity for oxygen ( $D_{T_{O_2}}$ ) of the tonometer is:-

$$D_{T_{O_2}} = \frac{C_{1_{O_2}} - C_{2_{O_2}}}{(P_{G_{O_2}} - \bar{P}_{T_{O_2}})} \cdot \frac{1}{(T_2 - T_1)}$$

where  $C_{1_{O_2}}$  = Oxygen content of blood in tonometer at time 1

$C_{2_{O_2}}$  = Oxygen content of blood in tonometer at time 2

$P_{G_{O_2}}$  = Oxygen tension of equilibrating gas

$\bar{P}_{T_{O_2}}$  = Mean oxygen tension of tonometer blood  
between times 1 and 2

$T_1$  = time 1 in minutes,  $T_2$  = time 2 in minutes.

To calculate  $D_{T_{O_2}}$ , therefore, these values must be obtained.  $C_{1_{O_2}}$  and  $C_{2_{O_2}}$  are calculated by determining the total oxygen content (by the method of Van Slyke and Neill, 1924) on blood samples taken at times 1 and 2, and multiplying these values by the volume of blood actually present in the tonometer during the period between times 1 to 2. The oxygen tension  $P_{G_{O_2}}$  is easily obtained from analysis of the effluent gas. The mean  $PO_2$  of tonometer blood is more difficult to obtain. However, if the  $PO_2$  at time 1 and at time 2 is measured and provided that these values are such that the mid zone of the oxyhaemoglobin dissociation curve is considered (which approximates to a straight line), the arithmetic mean  $PO_2$  can be used, again provided that the difference between the

$PO_2$  at time 1 and time 2 does not exceed 10 mm.Hg or so. This approach was therefore used to determine the diffusing capacity of the tonometer for oxygen and for carbon dioxide. In both cases the measurements were carried out when 10, 20, 30 and 40 mls. of blood were used in the tonometer. If the diffusing capacity is related to the available interface area between gas and blood, this would be expected to change with increasing blood volumes. The relationship is in fact complex, being essentially determined by the area of the sector ADBE minus the area of the circle of radius OE (Figure 31). The volume of blood on the other hand is related to the area AEBC, the dependent segment. The simple solution of determining these areas by planimetry on full-scale drawings was applied to the problem of determining the form of the relationship between the area AEBC (a linear relationship of the volume of blood introduced) and the area (ADBE minus area of circle radius OE). The results are plotted in Figure 32 along with the results of the diffusing capacity of the tonometer for oxygen, at the various volumes of blood in the tonometer. The results for both oxygen and carbon dioxide diffusing capacity are shown in Table I.

These results would therefore suggest that this new tonometer is capable of equilibrating 10 - 50 ml. samples of blood with gas mixtures efficiently and with little damage to the blood. The values for diffusing capacity at a volume of 10 mls. are some four times those given by Ravin and Briscoe (1964) for their bubble tonometer, using large bubbles



## TONOMETER DISCS

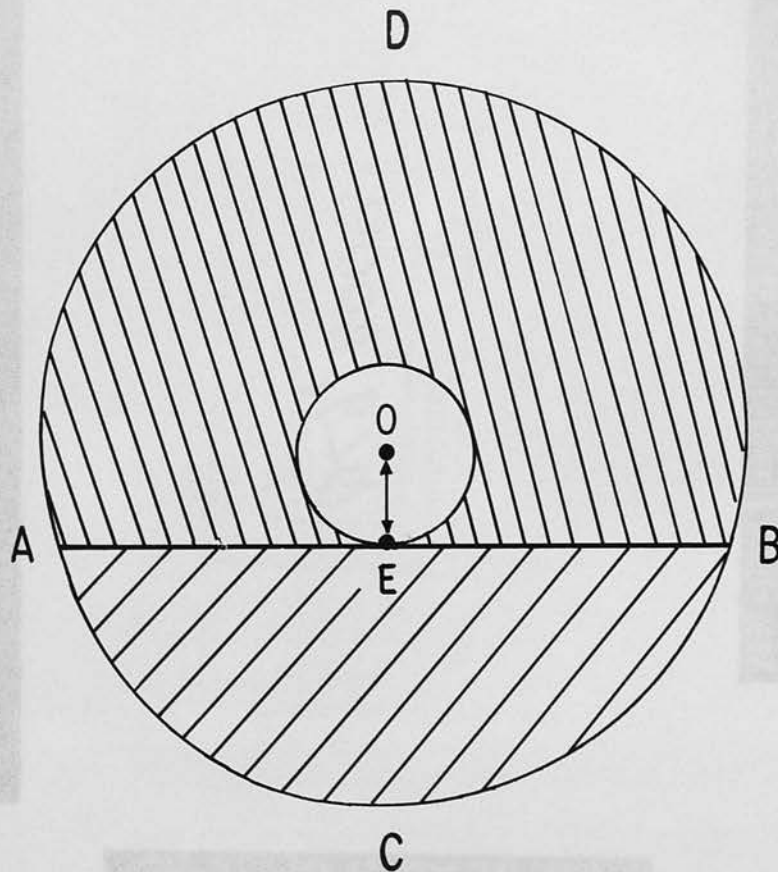


Figure 31

The geometry of the tonometer discs. The shaded area AEBC immersed in blood in the tonometer cylinder, the shaded area AEBD is the area of the disc covered by blood during rotation.

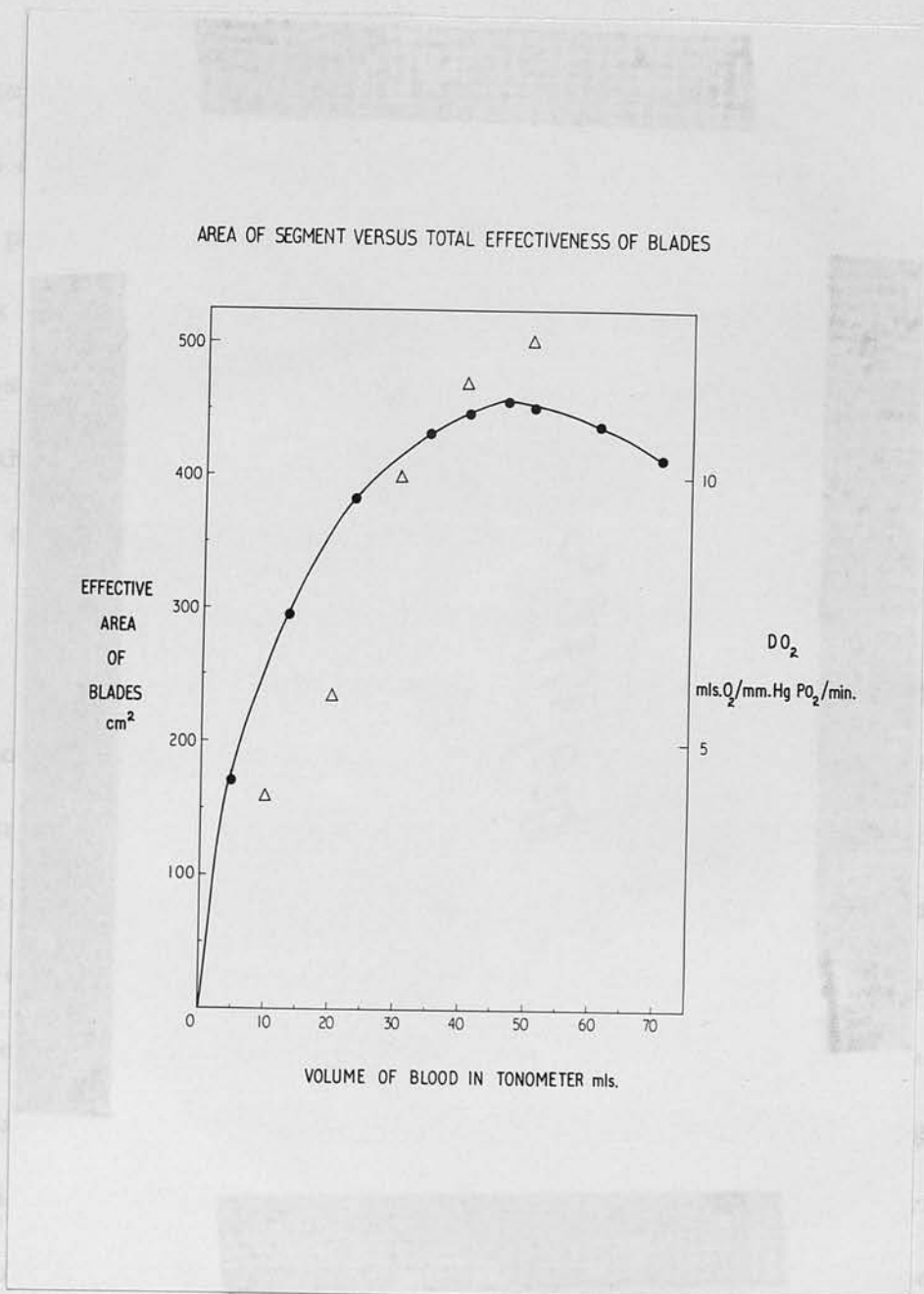


Figure 32

The relationship between the area of tonometer discs available for gas exchange (AEBD of Figure 31) and the volume of blood in the tonometer. The closed circles and continuous line represent this relationship. The open triangles are measurements of the oxygen diffusing capacity ( $DO_2$ ) of the tonometer, at various volumes of blood.

of the type they recommend. There is no other published work on such a detailed analysis of tonometer behaviour known to the author. The present tonometer is very much cheaper than the large rotating flask tonometer described by Fahri (1965) and has a much greater exposure of blood gas interface at a comparable rate of rotation than has the tonometers of both Fahri (1965), Lave (1951) and Hall (1960). It is extremely convenient in use.

#### 5. The Calibration of the Oxygen Electrode:

The electrode was standardised with "white spot" nitrogen as the low reference point, and humidified air, or blood which had been tonometered with air, as the high reference point. Air and nitrogen were introduced by 50 ml. syringes and the meter settings made when the readings were steady between 3 and 5 minutes later. When the oxygen electrode was used to measure the  $PO_2$  of gas mixtures, these samples were also introduced from 50 ml. syringes. These gas mixtures, consisting of nitrogen, oxygen and carbon dioxide, were analysed by the Lloyd-Haldane apparatus, with agreement to 0.03% between duplicate analyses. Before each reading on tonometered blood the  $PO_2$  electrodes were flushed with nitrogen, air and finally tonometer gas which immediately preceded the tonometer sample. The electrode cuvette was kept filled with 1:1000 solution of Roccal overnight.

The results of the calibration experiment are shown in Figure 33. The regression equation describing the relationship between tonometer gas

$PO_2$  and the electrode reading of  $PO_2$  are calculated in the form:-

$$\text{Electrode } PO_2 = A + B (\text{Tonometer gas } PO_2)$$

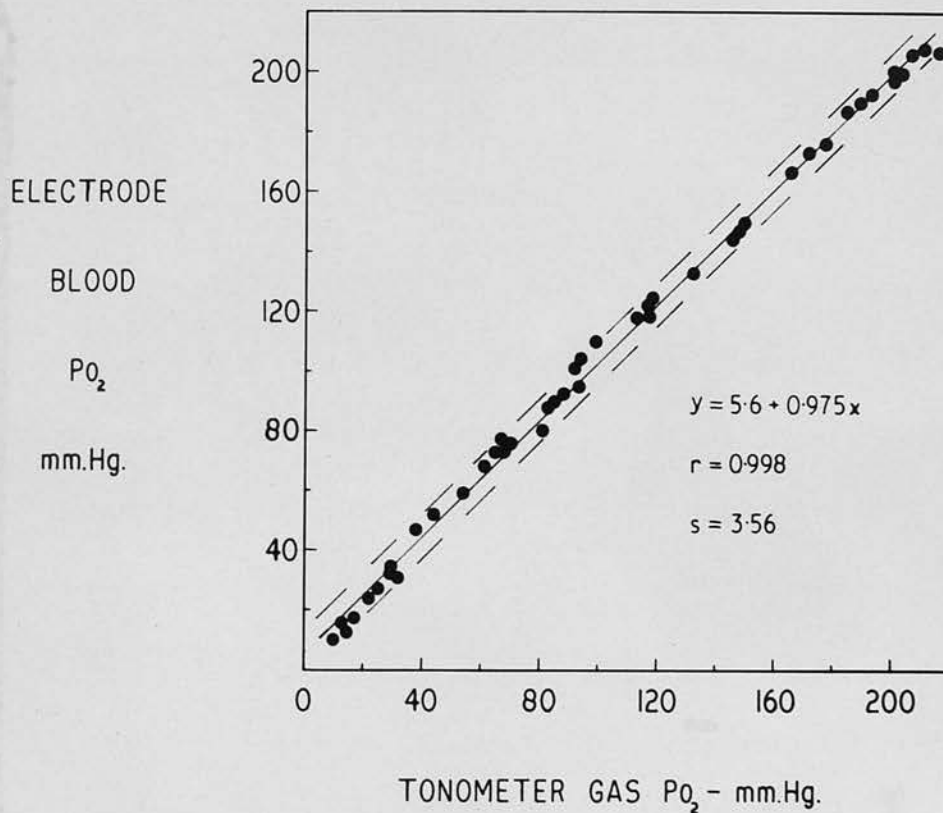


Figure 33

The calibration line of the Radiometer E5044  $PO_2$  electrode, using the new tonometer. The dotted lines are drawn at the 95% confidence limits. One reading on each sample.

The results are shown in Figure 33 and in Table 2, again as the

constants of regression equations relating electrode  $PO_2$  to the tonometer gas values, and also include the standard deviation about the regression line.



PO<sub>2</sub> and the electrode reading of PO<sub>2</sub> are calculated in the form:-

$$\text{Electrode PO}_2 = A + B (\text{Tonometer gas PO}_2)$$

The detailed equations, including one standard deviation about the regression line (Bailey, 1959) are shown in Table 2. The equations are calculated for results when nitrogen and moist air were used as the reference points, and when nitrogen and blood tonometered with air was used as a reference point. In Figure 34 results are also presented for an experiment where one operator carried out both PO<sub>2</sub> and PCO<sub>2</sub> measurements, and tonometry at a rate of one fresh tonometric gas mixture every 25 minutes. This required rapid and skilled performance of numerous tasks.

#### 6. The Calibration of the Carbon Dioxide Electrode:

The electrode was standardised with gas mixtures, of approximately 3% carbon dioxide in 17% oxygen and 9% carbon dioxide in 17% oxygen, the actual concentrations being determined by Lloyd-Haldane analysis. These mixtures were flushed through the cuvette of the carbon dioxide electrode for at least 10 minutes, all gas connections being by thick wall rubber tubing. Final meter settings were made with zero gas flow. Blood samples from the tonometer were introduced into the electrode after it had been flushed with tonometer gas.

The results are shown in Figure 35 and in Table 2, again as the constants of regression equations relating electrode PCO<sub>2</sub> to the tonometer gas values, and also include one standard deviation about the regression line.

ELECTRODE  
BLOOD  
PO<sub>2</sub>  
mm.Hg

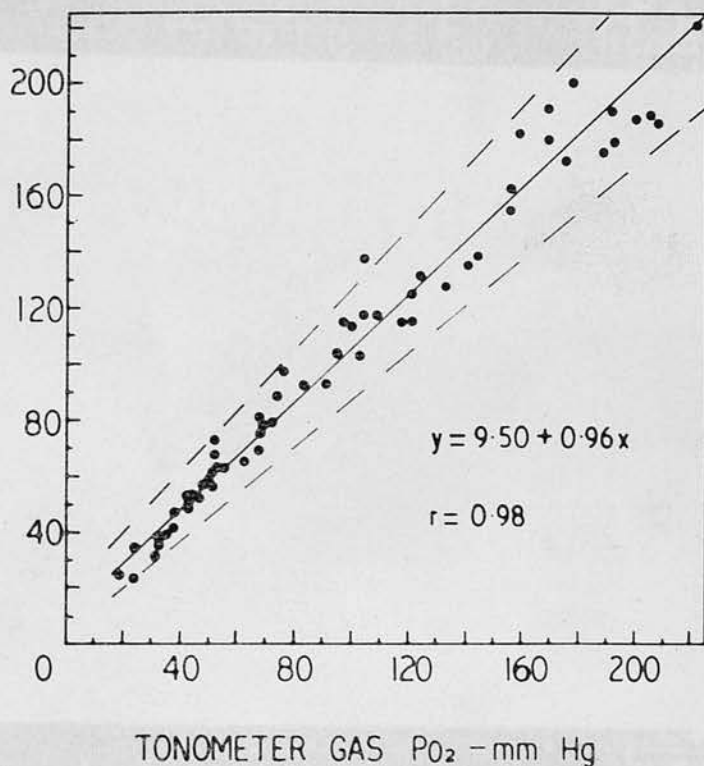


Figure 34

The calibration line of the Radiometer E5044 PO<sub>2</sub> electrode, using the new tonometer, under conditions of rapid use. The dotted lines are at the 95% confidence limits. One reading on each blood sample.

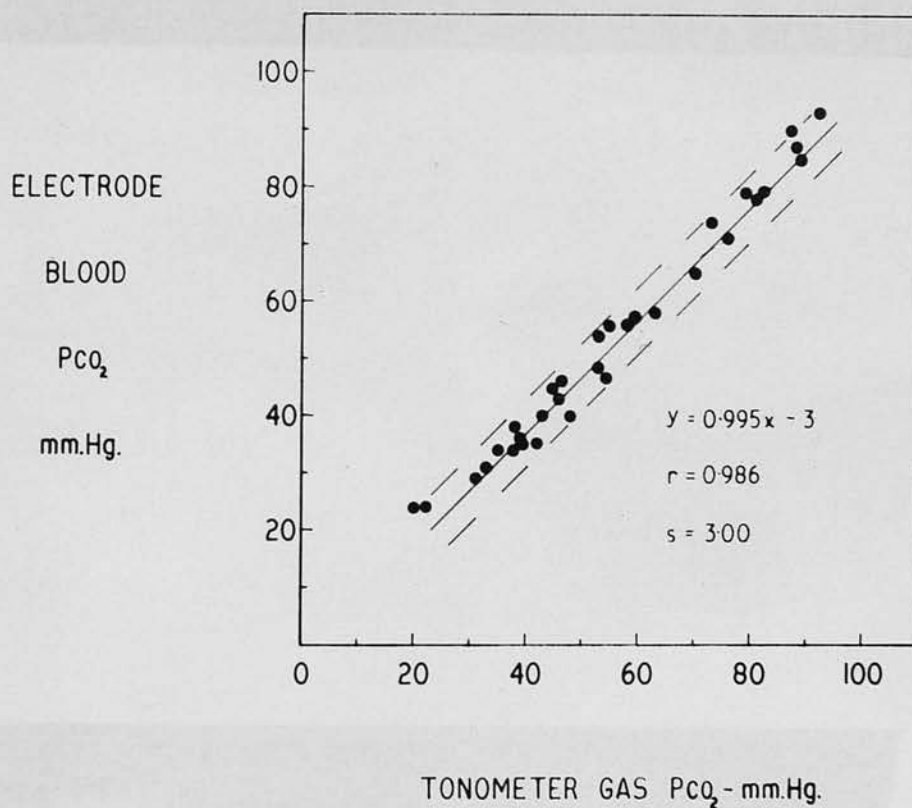


Figure 35

The calibration line of the Radiometer E5030 PCO<sub>2</sub> electrode using the new tonometer, with setting up on two gas mixtures. The dotted lines are at the 95% confidence limits. One reading on each blood sample.

In addition to the use of gas mixtures to standardise the electrode, the opportunity was taken to determine the effects of using tonometered blood as a standard. This was done by using two of the four tonometer samples, obtained during one morning or afternoon tonometer session, as standards and regarding the two interpolated carbon dioxide samples as "unknown". The results for this procedure using tonometered blood as standards, is also shown in Table 2 and in Figure 36.

#### 7. Discussion of Calibration Results:

The difference between the reading of the electrodes and the  $PO_2$  (or  $PCO_2$ ) of the tonometer gas, can be divided into two parts. The first, which is referred to as the systematic error, can be predicted from the coefficient and intercept of the regression equations in Table 2. It therefore follows that such systematic errors can be eliminated by use of equations derived from these calibration graphs. It is commonly considered that the blood gas ratio (the reading on blood divided by the reading on gas of the same  $PO_2$ ) is the only figure required to express the systematic error of a  $PO_2$  electrode. This ratio is not an adequate description of the systematic error of the electrode when used to measure the  $PO_2$  of blood in the range 0 - 200 mm.Hg considered here, for it assumes that the calibration graph passes through the origin. That this assumption is not valid is demonstrated by the equations in Table 2. The intercepts of the regression line for the oxygen electrode when used to measure gas mixtures is not significantly different from zero,



ELECTRODE  
BLOOD  
PCO<sub>2</sub>  
mm.Hg.

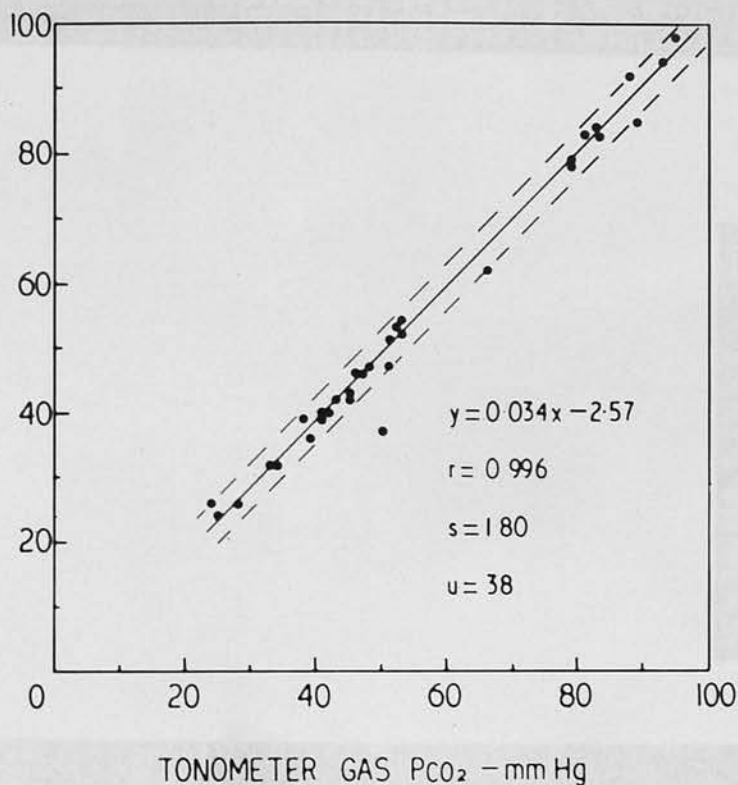


Figure 36

The calibration line of the Radiometer E5030 PCO<sub>2</sub> electrode, using the new tonometer, with setting up on two tonometered blood samples. The dotted lines are at the 95% confidence limits. One reading on each blood sample.

$$\text{Electrode } \text{PO}_2 = 7.37 + 0.97 \text{ Gas } \text{PO}_2 + 0.07 (\text{Gas } \text{PCO}_2)$$

i.e. this line does pass through the origin, but the intercept of the regression line for blood  $PO_2$  does have a significant value. It follows that the only method of eliminating the systematic error of this electrode, when used to measure blood  $PO_2$  in this range, is to use calibration equations of the type described here. A similar intercept in the equations for a similar micro-cathode unstirred electrode is described by Moran, Kettel and Cugell (1966).

The second part of the difference between the true reading and the electrode reading is the random error. This error is shown by the scatter which can be expressed as the standard deviation about the regression line. The 95% confidence limits are almost  $\pm$  twice this standard deviation, the true limits being so close to this as to be indistinguishable (Snedecor, 1956). The difference in values of standard deviation in the figures and in the table is that the results in the figures are based on only one reading on each blood sample. In practice (and in the rest of this study) the mean of two readings on the same sample is used. Thus the standard deviation about the line is divided by  $\sqrt{2}$  for the results given in the table.

The interaction of carbon dioxide on the reading of the oxygen electrode was determined in 60 experiments where the  $PO_2$  and  $PCO_2$  were measured both in gas and in blood. The multiple regression equation:-

$$\text{Electrode } PO_2 = 7.27 + 0.95 (\text{Gas } PO_2 + 0.07 (\text{Gas } PCO_2))$$

shows no significant improvement in error over the simple equation:-

Electrode  $PO_2 = 9.50 + 0.96 (\text{Gas } PO_2)$  which describes the same results.

With the  $PCO_2$  electrode it was found that the use of blood tonometered with gas reduced the 95% confidence limits of the equation, but made no significant difference to the regression coefficient or intercept. The routine practice of calibrating these  $PCO_2$  electrodes with gas mixtures only will not therefore produce any systematic errors, but will introduce greater random errors.

The errors observed in this study must be compared with those found by others. In Table 3 the results of previous work on the accuracy of oxygen electrodes is summarised and in Table 4 the same information is given for carbon dioxide electrodes.

It would appear that the most accurate  $PO_2$  electrode yet described is that of Bishop, Pincock, Hollyhock, Raine and Cole (1966) who give 95% confidence limits of  $\pm 2.2$  mm.Hg in the range 0 - 150 mm.Hg. This instrument was used with a digital voltmeter, of very high input impedance, and the authors feel that this instrument may indeed have contributed to this very high accuracy.

The results of Moran, Kettel and Cugel (1966) are very similar to those described in this study, for the Radiometer oxygen electrode, and these authors also emphasise that the regression line for blood, at lower tension ranges, does not pass through the origin. Carbon dioxide

electrodes have been little studied, as Table 4 emphasises. The most extensive results are those of Nunn (1964) which are not dissimilar to those found in the present study.

8. Conclusion:

The accuracy of measurement of both  $PO_2$  and  $PCO_2$  in blood, using Radiometer electrodes, is approximately  $\pm 4.4$  mm.Hg for oxygen and  $\pm 2.8$  mm.Hg for carbon dioxide, provided that tonometered blood is used to standardise both oxygen and carbon dioxide electrodes.

CHAPTER III

THE VENTILATORY RESPONSE TO CARBON

DIOXIDE - RESULTS



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CHAPTER III

THE VENTILATORY RESPONSE TO CARBON

DIOXIDE . RESULTS

## CHAPTER VII

### THE VENTILATORY RESPONSE TO CARBON

#### DIOXIDE : RESULTS

The results in this section fall into three parts. A description of the subjects and patients, and their pulmonary function, is followed by a description of the ventilatory response to carbon dioxide, in terms of arterial  $PCO_2$ ,  $PO_2$ , activity and  $PO_2$  in the main experiments in which work measurements were also made, and finally results in similar terms where the ventilation alone was measured in the subsidiary experiments.

#### THE VENTILATORY RESPONSE TO CARBON

##### DIOXIDE : RESULTS

The normal subjects were colleagues (1, 3, 6), three hospital inpatients (4, 5, 7) and one outpatient (2). None of them had suffered from disease of the heart or lungs, and only two (5, 7) were cigarette smokers. Subject 4 had recovered from an attack of renal colic, as had subject 5. Subject 7 had suffered from one epileptic fit for which no cause was found, and subject 2 was under treatment for haemochromatosis. Only subjects 1 and 6 had any experience of respiratory experiments, and none of the subjects was aware of the experimental protocol. All the patients suffered from severe obstructive chronic bronchitis and emphysema, of varying severity.

## CHAPTER VII

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#### DIOXIDE : RESULTS

The results in this section fall into three parts. A description of the subjects and patients, and their pulmonary function, is followed by a description of the ventilatory response to carbon dioxide, in terms of arterial  $\text{PCO}_2$ ,  $(\text{H}^+)$  activity and  $\text{PO}_2$  for the main experiments in which work measurements were also made, and finally results in similar terms where the ventilation alone was measured in the subsidiary experiments.

#### 1. Normal subjects and patients:

The normal subjects consisted of three colleagues (1, 3, 6), three hospital inpatients (4, 5, 7) and one outpatient (2). None of them had suffered from disease of the heart or lungs, and only two (5, 7) were cigarette smokers. Subject 4 had recovered from one attack of renal colic, as had subject 5. Subject 7 had suffered from one epileptic fit for which no cause was found, and subject 2 was under treatment for haemochromatosis. Only subjects 1 and 6 had any experience of respiratory experiments, and none of the subjects was aware of the experimental protocol. All the patients suffered from severe obstructive chronic bronchitis and emphysema, of varying severity.

They all gave a history of cough and sputum production for at least four years. These patients would all appear to lie clinically in Group B of Burrows, Fletcher, Heard, Jones and Wootliff (1966) and therefore they would be expected to have bronchitis and not emphysema as the major pathological abnormality. Patients 14 and 15 were in heart failure but were free of oedema, following Digoxin, at the time of the study, as were patients 18 to 25.

Details of age, sex, height, weight, body surface area, vital capacity (V.C.) ratio of residual volume to total lung capacity (RV/TLC), Forced Expiratory Volume ( $FEV_{1.0}$ ) and Forced Vital Capacity (FVC) are given in Table 5. This Table also includes values predicted for normal subjects of the same age, sex, height and weight (Cotes, 1965).

The clinical state and the  $FEV_{1.0}$  of the patients had been stable for at least one week prior to the study, and cases 11, 13, 14, and 15 were known to have blood gas tensions unchanged from those three months previously, when breathing air. None of the patients or control subjects had received carbonic anhydrase inhibitors.

The normal subjects all had lung volumes and  $FEV_{1.0}$  values within two standard deviations of the predicted normal value for their age, sex and height. The ratio of  $FEV/FVC$  was above 70% in all these normal subjects, who thus showed no evidence of airways obstruction. The bronchitic patients all had a value of  $FEV_{1.0}/FVC$



below 70%. The RV/TLC ratio was well above the predicted normal value in all patients and the VC was reduced. The normal subjects were all studied when breathing air, at the start of the study, except for subject 3 where some carbon dioxide was added to the inspired gas. Excluding this subject, therefore, the mean resting ventilation of the normal subjects was 9.8 litres/min. (BTPS) when breathing air, with a mean arterial  $PO_2$  of 92 mm.Hg,  $PCO_2$  of 40 mm.Hg, and  $(H^+)$  of 40 nanoMols/litre (pH 7.40).

The bronchitic patients in the main group of experiments had a mean resting ventilation, when breathing air, which ranged between 6.7 and 10.9 litres/min. (BTPS). These patients showed a wide range in arterial blood gas tensions when breathing air, with a  $PO_2$  from 97 to 41 mm.Hg.,  $PCO_2$  from 44 to 77 mm.Hg and  $(H^+)$  from 38 to 51 nanoMols/litre.

The ten patients in which ventilation alone was measured suffered from chronic bronchitis. In this group the arterial  $PO_2$ , when breathing air, ranged from 36 to 68 mm.Hg., the arterial  $PCO_2$  from 38 to 64 mm.Hg, and the arterial  $(H^+)$  from 34 to 41 nanoMols/litre. The resting ventilation varied from 5.8 litres/min (BTPS) to 10.5 litres/min. (BTPS).

The detailed results of tidal volume ( $V_T$ ) (litres BTPS), and minute volume ( $\dot{V}_E$ ) (litres/min., BTPS), along with the work data at the various values of arterial  $PO_2$  (mm.Hg),  $PCO_2$  (mm.Hg) and

( $H^+$ ) (nanoMols/litres) are given in Tables 6 - 21 for all the normal subjects and bronchitic patients in the main experiments. The results are presented as the mean values,  $\pm$  one standard deviation, at each value of arterial  $PO_2$ ,  $PCO_2$  and ( $H^+$ ).

## 2. Relationship Between Minute Volume and Arterial $PCO_2$ for the Main Experiments:

The detailed relationships between the minute volume of ventilation (litres/min. BTPS), with the values of arterial  $PCO_2$  are presented in Table 22 and with arterial ( $H^+$ ) in Table 23. These results are presented as the constants of the equation:-

$$\dot{V} = S_{CO_2} (PCO_2 - B_{CO_2})$$

for the arterial  $PCO_2$  values, in Table 22.  $\dot{V}$  is the minute volume of ventilation,  $S_{CO_2}$  is the slope of the ventilation/ $PCO_2$  line in litres/min. (BTPS)/mm.Hg increase in arterial  $PCO_2$ , and  $B_{CO_2}$  is the intercept of this regression line, when extrapolated to the  $PCO_2$  axis. One such equation is calculated for each of three levels of  $PO_2$ , at the high, medium and low levels, for each subject. The method of calculating the minute volume of ventilation, from the pneumotachygraph traces, as described in Chapter V, gives numerous values at each  $PCO_2$  level. The actual values of arterial  $PO_2$  at the three levels of  $PCO_2$  are shown in the Table. The equations were fitted by least squares regression, with the Elliott 803 computer. In addition to calculation of the regression coefficient  $S_{CO_2}$  and the intercept

( $S_{CO_2}$  ·  $B_{CO_2}$ ) the standard computer programme used also gave one standard deviation of ventilation about the regression line. The programme also carries out an analysis of variance on the regression and relates the reduction in the mean square deviation about the mean values of ventilation to the mean square deviation of ventilation values about the regression line. This ponderous (but exact) statement (Snedecor, 1956) can be summarised by calling this the "Efficiency" of the regression. It basically shows the gain in accuracy of prediction of a value of ventilation given a value of  $PCO_2$  and the regression equation, over that obtainable if one knew nothing of the value of  $PCO_2$  or of the regression equation.

The results are also shown in Figures 37 and 38, which show the actual levels of  $PCO_2$  at which the measurements of ventilation were made. A study of Table 22 shows that the slope of the "carbon dioxide response line" in the normal subjects varied from 1.06 to 4.32 litres/min. (BTPS)/mm.Hg  $PCO_2$ . It is apparent that the values of  $S_{CO_2}$  in the individual subjects are higher at the low  $PO_2$  values in two of the seven normal subjects, and the  $S_{CO_2}$  values at the high  $PO_2$  values being greatest in another two of the seven subjects.

The value of  $B_{CO_2}$ , the intercept on the carbon dioxide axis, varies between 18.6 and 43.3 mm.Hg in the normal subjects with a mean value of 32.0 mm.Hg.

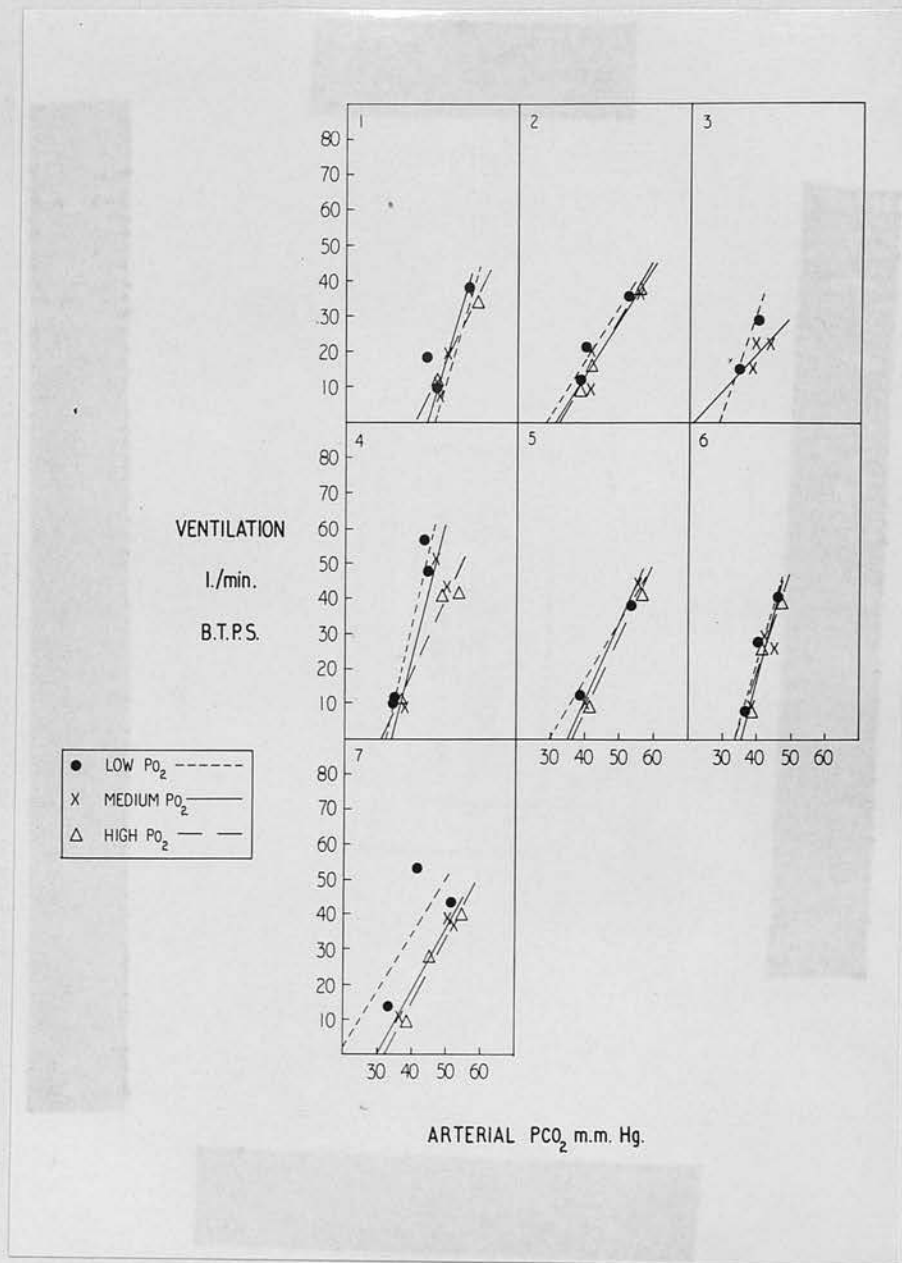


Figure 37

The relationship between the minute volume of ventilation and the arterial  $PCO_2$  in the main experiments, for the normal subjects.



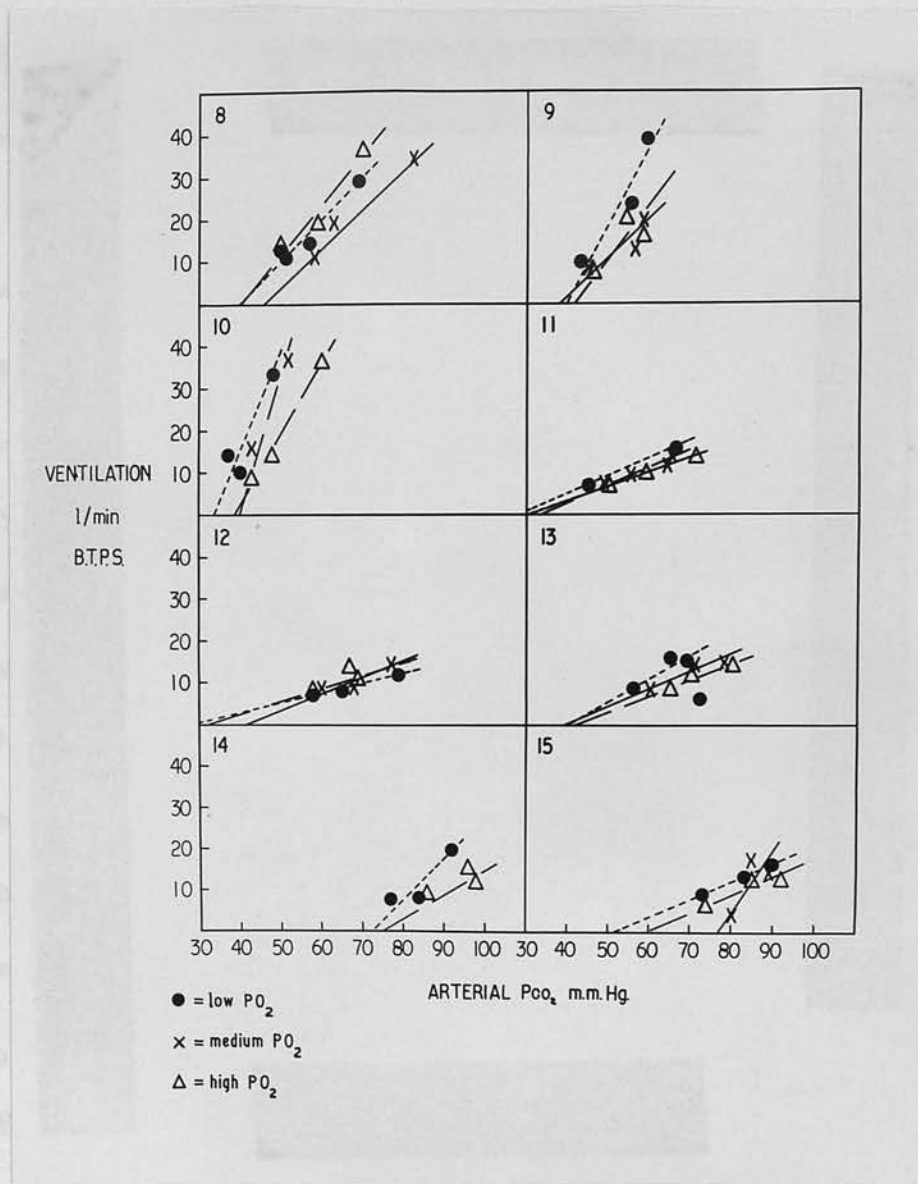


Figure 38

The relationship between the minute volume of ventilation and the arterial  $PCO_2$  in the main experiments, for the bronchitic patients.

The efficiency of the regression for the normal subjects varies between 98.2% to 33.6%, this lower value being associated with the lowest value of  $S_{CO_2}$  of 1.06 litres/min.(BTPS)/mm.Hg  $PCO_2$ . The low efficiency of the regression in this subject 3 for the medium  $PO_2$  values, is to be predicted from Figure 37, where it is seen that the range of both ventilation and arterial  $PCO_2$  in this patient were by far the smallest of any in the study.

In the bronchitic patients, the values of  $S_{CO_2}$  are considerably less than those in the normal subjects ranging from 3.04 to 0.22, mean 0.83 litres/min. (BTPS)/ mm.Hg.  $PCO_2$ . Again there is no obvious correlation between the arterial  $PO_2$  and the value of  $S_{CO_2}$ . Thus the  $S_{CO_2}$  value is greatest at the lowest  $PO_2$  in four patients of the eight, and greatest at the high  $PO_2$  in one patient. The values of  $B_{CO_2}$  vary greatly in the bronchitics, from 18.7 to 72.0, mean 40.5 mm.Hg.  $PCO_2$ . As Figure 38 shows, there is a slight tendency for low values of  $S_{CO_2}$  to be associated with the highest values of  $B_{CO_2}$ . The efficiency of the regression in these patients varies from 24.5% to 98.0% again the lower value (patient 12, high  $PO_2$ ) being associated with a small range of ventilation values. The efficiency therefore reflects the commonsense observation that a line can be more accurately drawn through points over a wide range of values than over a small range.

### 3. Relationship between Minute Volume and Arterial ( $H^+$ ) for the Main Experiments:

In Table 23 the same experimental results are described in terms of the relationship between the arterial ( $H^+$ ) activity and the ventilation.

The equation:  $V = S_H (H^+) - B_H$

is fitted, where:-

$V$  = Ventilation in litres/minute (BTPS),

and  $S_H$  = Slope of the regression line, as

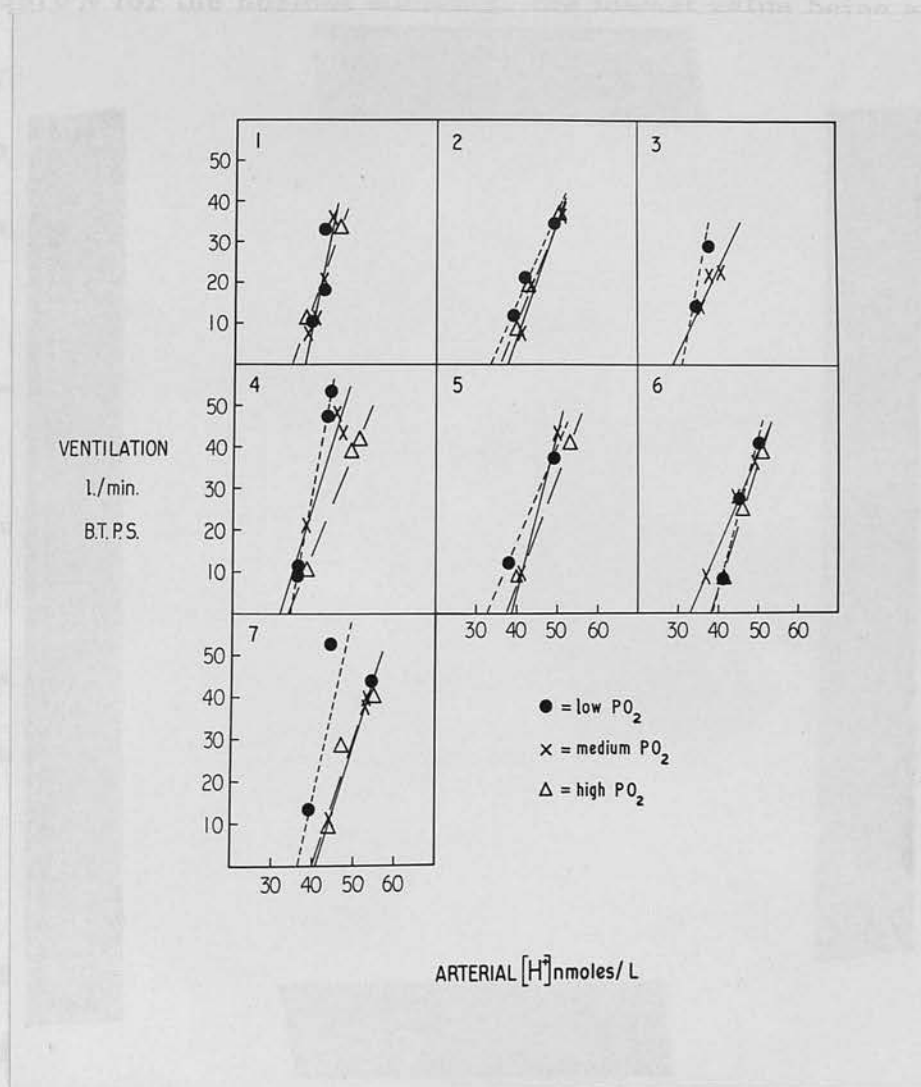
litres/min. (BTPS)/nanoMolar change

in arterial ( $H^+$ ) activity, and  $B_H$  is the intercept on the ( $H^+$ ) axis.

Again values of one standard deviation about the regression line, and the efficiency of the regression are included, as in Table 23. One equation has been calculated for each of the three levels of  $PO_2$  for each subject.

For the normal subjects,  $S_H$  varied from 1.35 to 5.60, mean 3.29 litres/min. (BTPS)/nanoMol/litre. The values of  $B_H$  for these subjects ranged from 22.8 to 40.6, mean 34.6 nanoMols/litre. As for the values of  $S_{CO_2}$ , there is no obvious relationship between  $S_H$  and the  $PO_2$  level, in these normal subjects (Figure 39).

The bronchitic patients have values of  $S_H$  varying between 6.83 and 0.26, mean 1.42 litres/min. (BTPS)/nanoMol/litre. The values of  $B_H$  in these patients varied from 8.7 to 44.4, mean 30.7 nanoMols/litre.



**Figure 39**

The relationship between the minute volume of ventilation and the arterial ( $H^+$ ) in the main experiments for the normal subjects.



The efficiency of these regression equations varied between 98.1% to 35.0% for the normal subjects, the lowest value being at the low oxygen levels of subject 7 and from 98.1 to 17.2% in the bronchitic subjects, this lowest value again being associated with a very small range of  $(H^+)$  and ventilation values (Figure 40).

#### 4. Relationship Between the Minute Volume and Arterial $PCO_2$ in the Subsidiary Experiments:

In these experiments, carried out in subjects 16 - 25, the minute volume of ventilation was measured by collection of expired gas in a Tissot spirometer, under similar "isoxic" conditions, during carbon dioxide inhalation. The results, expressed as values of minute volume, at various levels of arterial  $PO_2$  and  $PCO_2$ ,  $(H^+)$  and  $(HCO_3^-)$  are shown in Tables 24 - 34 for each subject.

In addition, the results are presented graphically in Figure 41. In these experiments an attempt was made to study two isoxic levels designated low  $PO_2$  and high  $PO_2$  respectively. The accuracy with which these aims were achieved is shown in the  $PO_2$  figures in Table 35. Regression lines of ventilation against arterial  $PCO_2$  are calculated for the high and low  $PO_2$  levels, and these lines are drawn in the figure. The constants of these regression lines, expressed in terms of the equation:

$$V = S_{CO_2} (PCO_2 - B_{CO_2})$$

are shown in Table 35. Also in this table are given details of the number of observations, the arterial  $PO_2$ , and the standard error of the coefficient,  $S_{CO_2}$  and

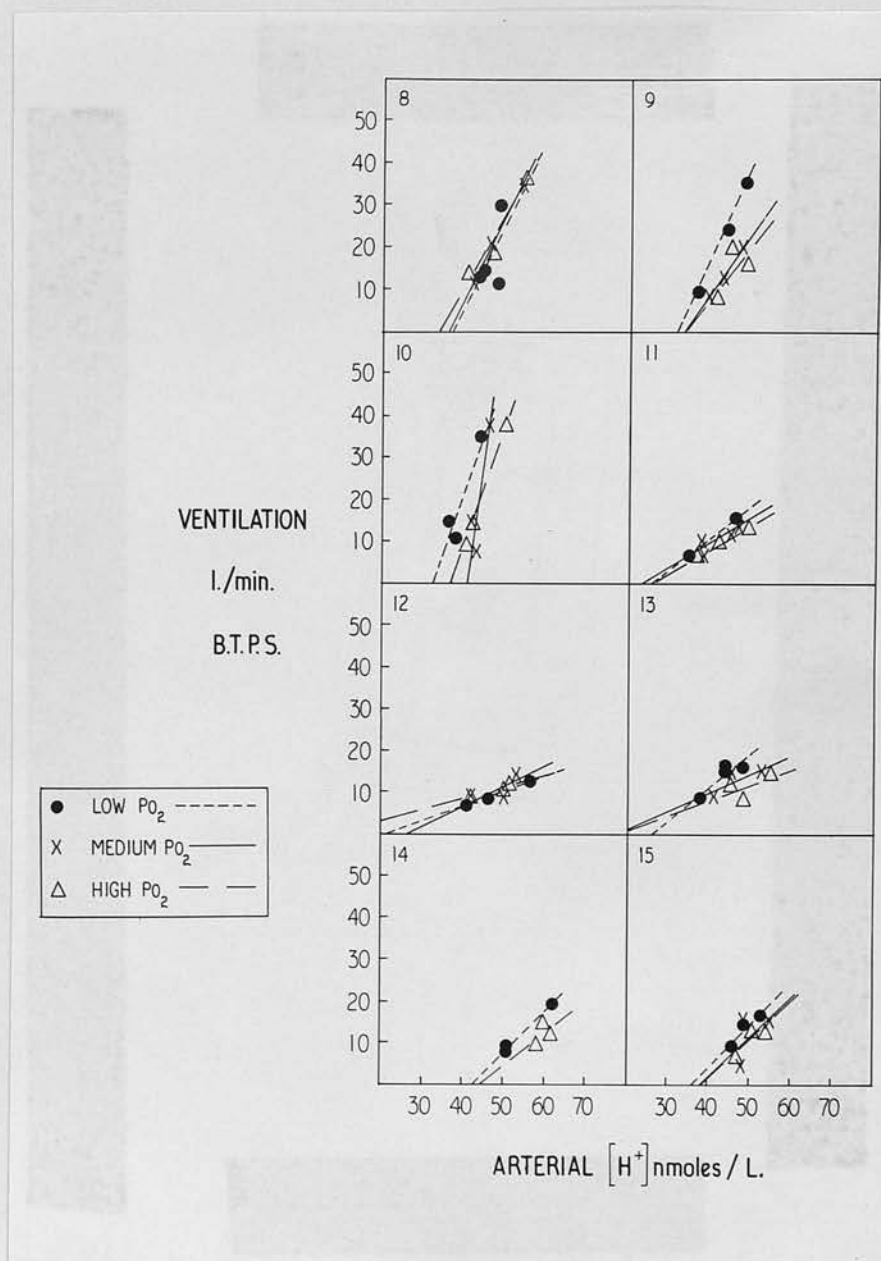


Figure 40

The relationship between the minute volume of ventilation and the arterial ( $H^+$ ) in the main experiments, for the bronchitic patients.

The relationship between the minute volume of ventilation and the arterial  $PCO_2$  in the subsidiary experiments, in bronchitic patients.

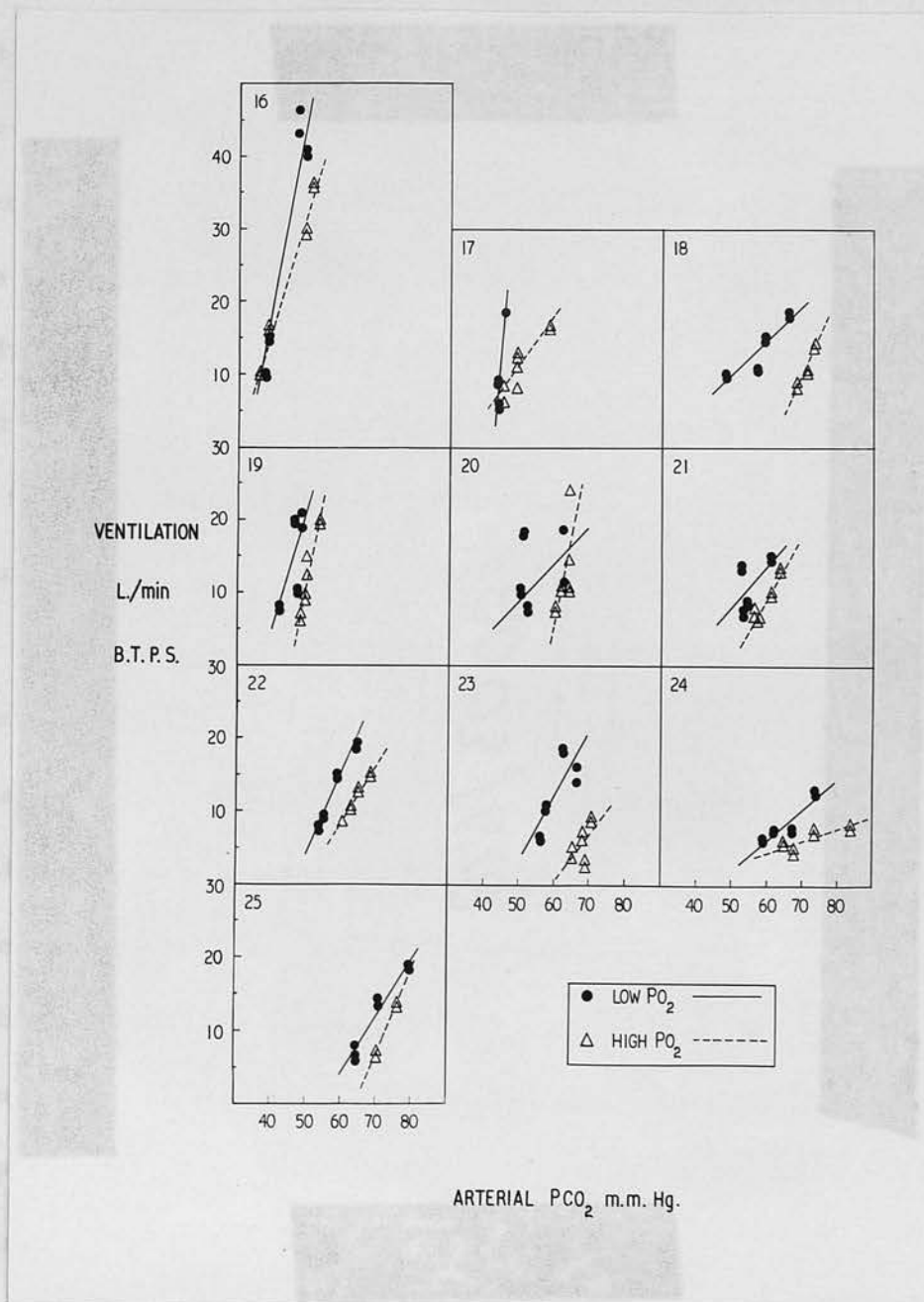


Figure 41

The relationship between the minute volume of ventilation and the arterial  $PCO_2$  in the subsidiary experiments, in bronchitic patients.

the value of one standard deviation about the regression line, with the correlation coefficient and its probability value. These equations were calculated using a desk calculator, and analysis of variance of the regression relationship was not carried out. In these experiments only two "isoxic" ventilation/ $\text{PCO}_2$  lines were drawn, and particular care was taken to try and maintain isoxic conditions, particularly on the "low  $\text{PO}_2$ " line. The arterial  $\text{PO}_2$  values varied between 4 and 15 mm.Hg in these lines at low  $\text{PO}_2$  levels.

The analysis of these results by means of the equation

$V = S_{\text{CO}_2} (\text{PCO}_2 - B_{\text{CO}_2})$  as shown in the figures, shows that the linear regression is significant for 17 of the 20 lines. It is obvious that the Oxford concept of a common value for " $B_{\text{CO}_2}$ " for any isoxic lines on the same patient, only applies to three of the present ten patients (cases 16, 23 and 24). In this respect these results differ from those in the main experiments where isoxic lines did appear to approximate to a common value of  $B_{\text{CO}_2}$  in six of the eight patients (cases 8, 9, 10, 11, 13, 14).

In the absence of a common value for  $B_{\text{CO}_2}$  between the two isoxic lines, therefore, it is apparent that the arterial  $\text{PO}_2$  must affect  $B_{\text{CO}_2}$  although not necessarily in the same way in each of these patients. It therefore is not valid to consider the effects of hypoxia on  $S_{\text{CO}_2}$  alone.



The values of  $S_{CO_2}$  in these ten patients varied between 2.54 to 0.16 litres/min/mm.Hg  $PCO_2$  for high  $PO_2$  lines, and between 5.59 and 0.42 litres/min/mm.Hg  $PCO_2$  for the low  $PO_2$  lines. There is no significant difference between the mean values of  $S_{CO_2}$  for the high  $PO_2$  lines and the low  $PO_2$  lines, in these patients ( $P > 0.10$ ).

## CHAPTER VIII

### THE YEAST-LEAST RESPONSE TO CARBON DIOXIDE:

#### DISCUSSION

## CHAPTER VIII

### THE VENTILATORY RESPONSE TO CARBON DIOXIDE:

#### DISCUSSION

The primary aim of the present study was to apply the technique which was developed at the Oxford School to study the ventilatory response to carbon dioxide inhalation in bronchitic patients with mild to moderate emphysema. These workers (Lloyd, Jukes and Campbell, 1961)

#### CHAPTER VIII

have demonstrated that a linear relationship exists in normal young men between the inspired (or arterial)  $PCO_2$  and the minute volume. THE VENTILATORY RESPONSE TO CARBON DIOXIDE:

The values for  $\dot{V}_E$  were generally above the resting levels, to ventilation levels of 10-15 l/min. Their work, in fact, confirmed the original studies of Nadelson and Smith (1952). A

#### DISCUSSION

smaller tidal volume was used in this study, but requires justification in the case of severe bronchitic patients.

#### 1. The Relationship Between Ventilation and Arterial $PCO_2$

The exact form of the relationship can only be determined by repeated studies of ventilation to steady state conditions, with measurement of arterial  $PCO_2$  at a constant  $PO_2$ . Such studies are more difficult to perform in patients with severe emphysema, but have only been reported in a very

## C H A P T E R V I I I

### THE VENTILATORY RESPONSE TO CARBON DIOXIDE:

#### DISCUSSION

The primary idea behind this present study was to apply the isoxic acute steady state method of the Oxford School to study the ventilatory response to carbon dioxide inhalation in bronchitic patients with respiratory failure. These workers (Lloyd, Jukes and Cunningham, 1958; Cunningham, Shaw, Lahiri and Lloyd, 1961) have established that a linear relationship exists in normal young men between the arterial (or alveolar)  $\text{PCO}_2$  and the minute volume, for values of  $\text{PCO}_2$  from 2 mm.Hg above the resting levels, to ventilation levels of about 80 litres/minute. Their work, in fact, confirms the earlier studies of Nielsen and Smith (1952). A similar form of analysis has been used in this study, but requires justification in its application to the bronchitic patient.

#### 1. The Relationship Between Ventilation and Arterial $\text{PCO}_2$ :

The exact form of this relationship can only be determined by repeated studies of ventilation in steady state conditions, with many small increments of arterial  $\text{PCO}_2$ , at a constant  $\text{PO}_2$ . Such studies are obviously impracticable in patients with severe respiratory failure, and, indeed, have only been reported in a very

small number of normal people, using alveolar gas pressures and not values of  $PO_2$ ,  $PCO_2$  and  $(H^+)$  in arterial blood. The linear relationship referred to above was also found by Falchuk, Lamb and Tenney (1966), in the upper ranges of  $PCO_2$ , in their three normal subjects under conditions of normal acid base balance.

This technique of the steady state carbon dioxide response has been used most extensively by the Oxford School, who have employed the technique to analyse the effects of hypoxia (affecting the slope of the relationship,  $S$ ) and metabolic acidosis (affecting the position of the intercept on the  $PCO_2$  axis ( $B$ ) (Figure 1)). Although there can be little disagreement with the general trend of these observations, the extensive mathematical treatment used by the Oxford workers (Lloyd and Cunningham, 1963) leaves most respiratory physiologists in the position of preferring "to think in graphical terms as long as the individual algebraic parameters lack clear definition with specific mechanisms" (Kellogg, 1964).

The use of such a linear relationship (determined at high levels of  $PCO_2$ ) to characterise the chemical control of ventilation at resting levels, is criticised by Dejours, Puccinelli, Armand and Ducharry (1965). These authors base much of their criticism upon the common practice of equating alveolar and arterial  $PCO_2$  levels at low ventilation values, and point out that the accuracy of measurement



of either of these two levels is no better than 1 mm.Hg. I would entirely agree with this criticism, as Chapter VI will have emphasised. Their other criticisms are directed to the fallacy regarding the ventilatory increment, or the alveolar ventilation ratio (as used by Gray), as measuring the output of the respiratory centre, and they include measurements of respiratory work in their strictures. It appears to the present author that much of this criticism is essentially directed to the philosophical meaning of "carbon dioxide threshold and sensitivity". Discussion of this topic appears relatively sterile, and I submit that much of this sterility may be avoided if carefully defined experimental measurements are compared in two situations. The aim of this study is to attempt to ascertain the reason for the difference in response to carbon dioxide inhalation in normal subjects and in patients with respiratory failure. By applying the same experimental situation to each of these groups, and by measuring the responses in the same way, it appears that some insight may thereby be gained into the differences in chemical control mechanisms. The carbon dioxide response curve, using relatively high levels of carbon dioxide, appears particularly valid in this present context, for of course high levels of arterial  $\text{PCO}_2$  are the very hallmark of the patient with ventilatory failure.

The linear regression equations described in Chapter VII relating minute volume to arterial  $\text{PCO}$  and  $(\text{H}^+)$  are the simplest

mathematical model of such a relationship. The adequacy of this approach is shown by the statistical data in Tables 22 and 23. These equations have an efficiency of over 80% in the reduction produced by the regression in the mean square deviation about the mean, for 16 of the 20 equations for the normal subjects, and for 12 of the 23 equations involving the bronchitic patients, as far as the ventilation/ $\text{PCO}_2$  relationship is concerned. In only four of these equations was the efficiency of the regression less than 50%. The tables use all the experimental data obtained. It must be emphasised that the same type of linear regression analysis has been applied to data from both normal and bronchitic subjects.

## 2. Acid Base Balance During Carbon Dioxide Inhalation:

The relationship between the arterial  $\text{PCO}_2$  and the arterial  $(\text{H}^+)$  for the main experiments (involving measurements of work of breathing) are shown in Figure 42. This figure is a plot of the Henderson (1908) expression for the mass action law, applied to the dissociation of carbonic acid, as no logarithms are involved. The results for the normal subjects fall within the significance bands described by Brackett, Cohen and Schwartz (1965) for the "whole body carbon dioxide titration curve" in normal men. By this expression these authors described the relationship between  $\text{PCO}_2$  and  $(\text{H}^+)$  (or bicarbonate) in arterial blood when the subject is given carbon dioxide to breathe. This relationship, determined by measurements made on

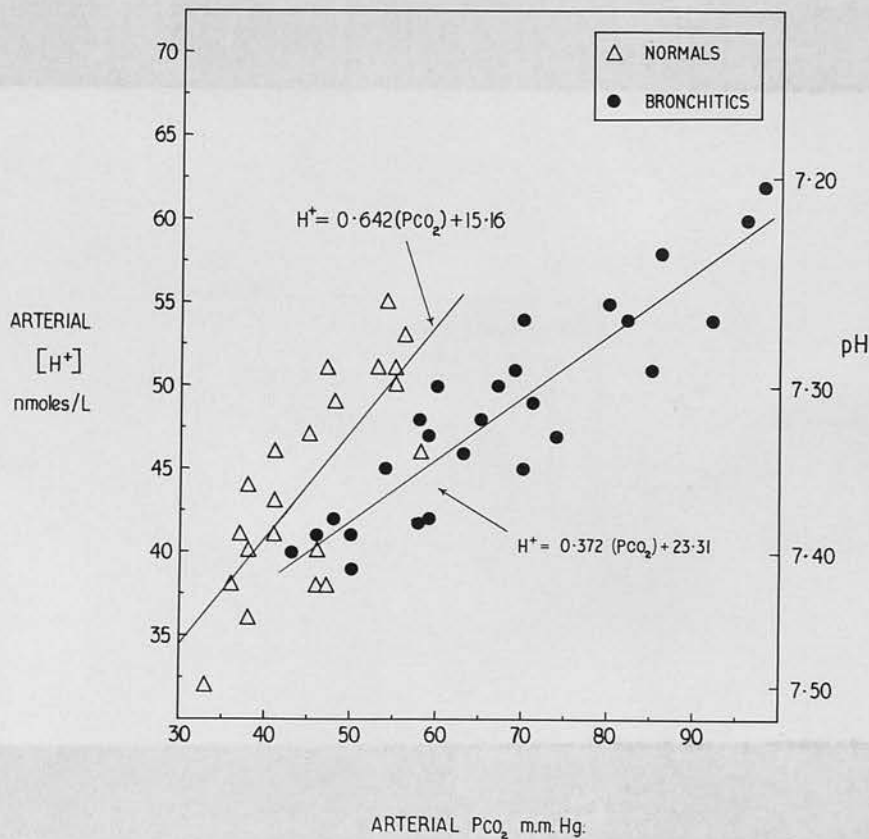


Figure 42

The relationship between the arterial ( $H^+$ ) and the arterial  $PCO_2$ , during the inhalation of carbon dioxide mixtures for 20 minute periods in the main experiments. The arterial  $PO_2$  was above 100mm.Hg for all the points plotted. The whole body carbon dioxide titration curve.

blood exposed to carbon dioxide in vivo, is to be contrasted by the classical "carbon dioxide dissociation curve" of physiologists, determined by exposing blood to varying tensions of carbon dioxide in vitro. The two curves are not identical, and the discussion as to which is most relevant in clinical practice is at the heart of the "great Transatlantic acid base debate" between Boston and Copenhagen (Relman, 1966; Sigaard-Andersen, 1966; Schwartz, 1966).

The relationship between ( $H^+$ ) and  $PCO_2$  shown in Figure 42 for normal subjects does not differ significantly ( $P > 0.05$ ) from the line calculated by Gray (1950) from the results of Shock and Hastings (1935). Figure 42 also shows that these bronchitic patients also have a relationship between  $PCO_2$  and ( $H^+$ ) in the arterial blood which differs significantly from that in the normal subjects. The results from these bronchitic patients are nearly all within the confidence limits found by Schwartz, Brackett and Cohen (1965) for dogs rendered chronically hypercapnic over five to seven days in an environmental chamber. This difference between the "acute" whole body carbon dioxide titration curve for normal subjects and the "acute on chronic" curve found in these patients (and in chronically hypercapnic dogs) depends upon the increase in bicarbonate reabsorption by the renal tubules in chronic hypercapnia (Schwartz, Falbriand and Lemieux, 1959).

The results in the bronchitic patients demonstrate that the human response to chronic carbon dioxide retention is essentially



similar to that in dogs, at least in terms of the blood acid base balance. Schwartz, Brackett and Cohen (1965) point out that a knowledge of this relationship between  $\text{PCO}_2$  and  $(\text{H}^+)$  in chronic hypercapnia could be useful in the clinical management of acute exacerbations of respiratory failure. Refsum (1964) has described a similar range of values for  $\text{PCO}_2$  and  $(\text{H}^+)$  concentrations in the arterial blood of patients with chronic respiratory failure, measured during acute exacerbations of the disease. These results are not strictly comparable for infection, severe hypoxia and the role of drugs are all somewhat uncertain variables in such acutely ill patients.

### 3. Acid Base Status and Ventilatory Control:

The results are described by the regression equations, in which the slope of the ventilation/ $\text{PCO}_2$  line ( $S_{\text{CO}_2}$ ) and the slope of the ventilation  $(\text{H}^+)$  line ( $S_{\text{H}}$ ) can be regarded as expressions of the sensitivity to carbon dioxide and  $(\text{H}^+)$  as ventilatory stimulants. The values  $B_{\text{CO}_2}$  and  $B_{\text{H}}$ , the intercepts on the zero ventilation axis, are convenient descriptive terms indicating the position of the lines but are not the physiological "threshold", for the actual response line becomes J shaped near the resting ventilation point (Nielsen and Smith, 1951) and these intercepts are merely extrapolations from the linear part of the relationships.

The values of  $S_{\text{CO}_2}$  in the normal subjects are significantly greater than  $S_{\text{CO}_2}$  in the patients with bronchitis, for all three levels of  $\text{PO}_2$  ( $0.001 > P$ ,  $0.02 > P > 0.01$ ,  $0.01 > P > 0.005$ ), thereby demonstrating

that increased tolerance to carbon dioxide as a ventilatory stimulus first noted by Scott in 1920. He attributed this result to increased buffering of the acidic properties of carbon dioxide in the blood and tissues of the chronically hypercapnic patient. This interpretation was in keeping with the Reaction Theory of Winterstein (1921).

The effect of blood buffering can be examined in this study by comparing the values of  $S_H$ , the ventilatory response to unit increment in arterial ( $H^+$ ), in the normal subjects and the patients with bronchitis. The values of  $S_H$  are significantly lower in the bronchitic patients for the high and low  $PO_2$  data ( $0.005 > P > 0.001$ ,  $0.01 > P > 0.005$ ) but not significantly different for the data at the medium  $PO_2$  level ( $0.10 > P > 0.05$ ).

The weight of evidence from these results, therefore, does not support the idea that the decreased ventilatory response to carbon dioxide inhalation in these patients can be attributed to the increased buffering of carbon dioxide in the arterial blood. The response is still depressed even when expressed in terms of sensitivity to blood ( $H^+$ ) activity.

The subsidiary experiments were carried out after the results of the main experiments were analysed, in order to determine if the conclusions of these main experiments, at least in regard to the acid base status and the control of ventilation, could be sustained in other cases. Ten cases of chronic bronchitis were studied, with a similar

experimental protocol, but with greater care taken to maintenance of isoxic conditions, particularly on the "low  $PO_2$ " ventilation/ $PCO_2$  response line. Only two levels of  $PO_2$  were studied, a "low" level ( $PO_2$  33 to 68 mm.Hg) and a "high" level ( $PO_2$  102 to 252 mm.Hg), with deviations of between 4 and 15 mm.Hg in  $PO_2$  levels in the "low" isoxic lines in the ten patients (see Table 35).

Comparison of the values of  $S_{CO_2}$  for these ten patients (numbers 16 - 25) with those of the normal subjects (numbers 1 - 7) reveals a significant difference in mean values ( $0.05 > P > 0.02$ ) for the "high"  $PO_2$  lines, but an insignificant difference ( $P > 0.1$ ) for the "Low"  $PO_2$  lines. However, the difference in  $S_H$  is significant between the normal subjects and these bronchitic patients for both levels of  $PO_2$  ( $0.01 > P > 0.002$  for the "high"  $PO_2$  lines, and  $0.05 > P > 0.02$  for the "low"  $PO_2$  lines). These findings therefore strongly support the concept that the increased buffering of  $(H^+)$  ion changes in blood following carbon dioxide inhalation in the bronchitic is an inadequate explanation for the decrease in sensitivity to inhaled carbon dioxide as a ventilatory stimulant, which is characteristic of the bronchitic patients.

#### 4. Acid Base Status at Constant Ventilation:

A comparison of ventilatory sensitivity to arterial  $(H^+)$  activity and  $PCO_2$ , in varying states of acid base balance, can be made by calculating the values of these two stimuli at a standard level of ventilation from carbon dioxide response curves. Previous

studies of this problem (Cunningham, Shaw, Lahiri and Lloyd, 1961; Kellogg, 1963) have concentrated upon the extrapolation of a linear carbon dioxide response curve to zero ventilation. However, I have preferred to work with a standard ventilation of 10 litres/minute, for not only is this nearer to the actual value of the resting ventilation, but also the values of  $(H^+)$  and  $PCO_2$  are little affected by the variable slope of the carbon dioxide response line which occurs in the bronchitic patients.

By substitution of the value 10 litres/minute in the equations of Tables 22 and 23, the values of arterial  $(H^+)$  and  $PCO_2$  in the present normal subjects and bronchitic patients are obtained directly. Similar results from the ventilatory response to carbon dioxide in patients with severe metabolic acidosis due to renal failure (Anderton, Harris and Robson, 1965), normal subjects (Cunningham et al, 1957; Katsaros et al, 1960; Kellogg, 1963), experimental ammonium chloride acidosis (Cunningham et al, 1957), experimental bicarbonate alkalosis (Katsaros et al, 1960) and altitude acclimatisation (Kellogg, 1963) are all available from the literature, and can be expressed in terms of arterial  $(H^+)$  and  $PCO_2$  at a ventilation of 10 litres/minute, by use of the Sigaard-Andersen alignment nomogram (Sigaard-Andersen, 1963). In all cases in which this comparison is made, the arterial  $PO_2$  was maintained above 100 mm.Hg.



The results of these calculations are shown in Figure 43 which is a plot of the arterial ( $H^+$ ) against the arterial  $PCO_2$  for a ventilation of 10 litres/minute in these various conditions. Two regression lines are calculated, one relating ( $H^+$ ) to  $PCO_2$  in states of metabolic acidosis, normal acid base balance, and metabolic alkalosis. This "metabolic" line is contrasted with the "respiratory" line, which is drawn through points obtained from patients with respiratory acidosis, normal acid base values, and respiratory alkalosis (altitude acclimatisation).

It would appear from Figure 43 that the arterial ( $H^+$ ) concentration and  $PCO_2$  values can combine in different ways to produce the same level of ventilation. This problem is illustrated arithmetically in Table 36. The values of arterial ( $H^+$ ) concentration and  $PCO_2$  at the ventilation of 10 litres/minute, are calculated for the five conditions, respiratory alkalosis and acidosis, normal subjects and metabolic alkalosis and acidosis using the regression equations of Figure 43. The simplest assumption is made, namely that these values can be combined additively to give a value for the ventilatory stimulus. On this crude basis, therefore, it is seen that whereas the metabolic disorders give values of ventilatory stimulus which are not far removed from the normal, the respiratory disorders show a wide spectrum, from increased sensitivity in the altitude acclimatised with a respiratory alkalosis, to a much decreased sensitivity to the combined stimulus of arterial acidity and hypercapnia in the bronchitic.

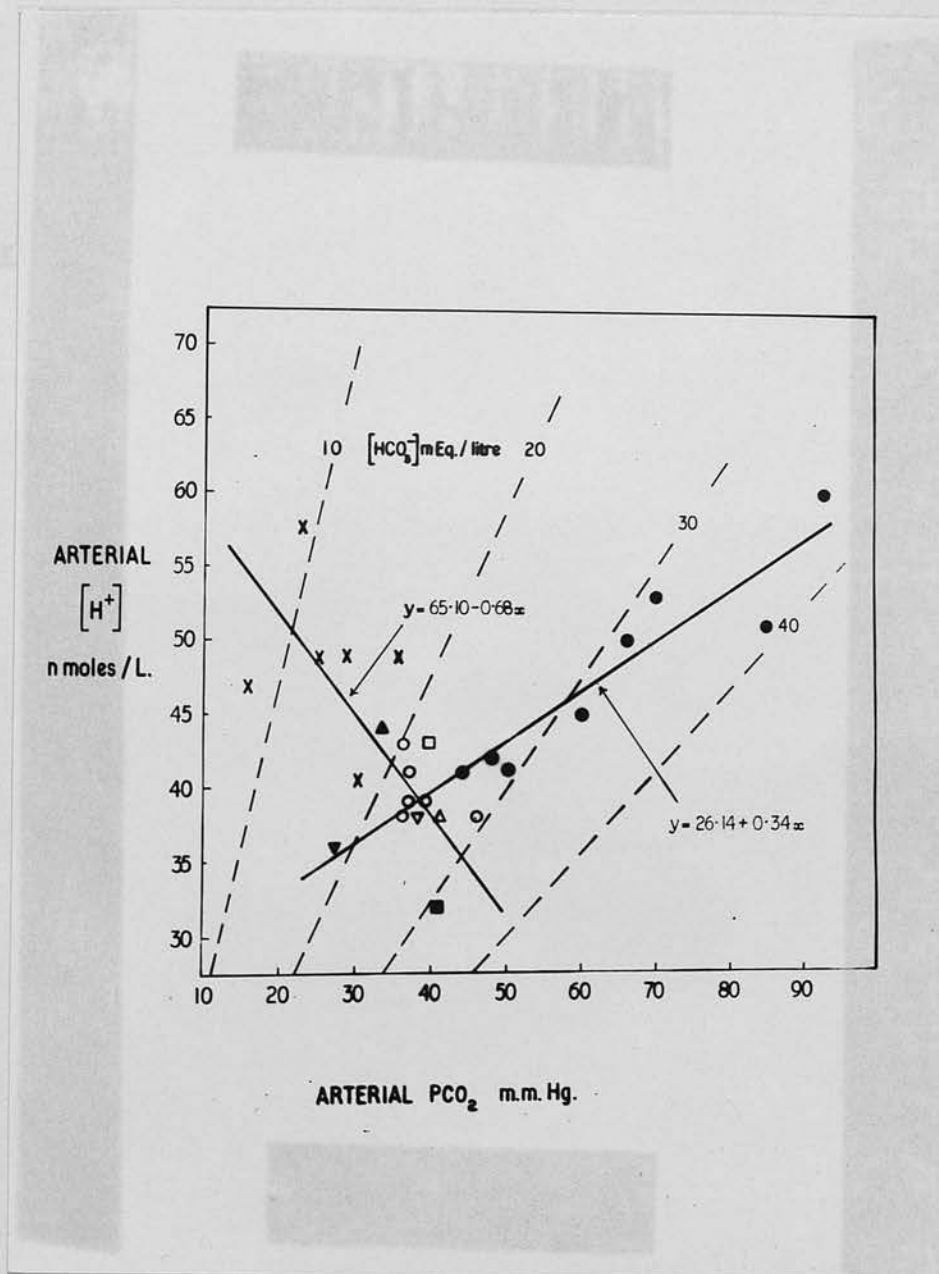


Figure 43

The relationship between arterial ( $H^+$ ) and arterial  $PCO_2$  at a constant ventilation of 10 litres/min. in various acid base derangements, when the arterial  $PO_2$  is over 90 mm.Hg.

- = Individual normal subjects (this study)
- = Normal values (mean) Katsaros et al (1960)
- △ = Normal values (mean) Cunningham et al (1961)
- ▽ = Normal values (mean) Kellogg (1960).
- = Individual values in chronic bronchitis and respiratory failure (this study)

continued/...

Figure 43 continued:

- X = Individual values in chronic renal acidosis (Anderton et al, 1965).
- ▨ = Mean values in acute experimental metabolic acidosis (Cunningham et al, 1961)
- Δ = Mean values in experimental metabolic acidosis (Cunningham et al, 1961)
- ▽ = Mean values in respiratory alkalosis (altitude acclimatisation) Kellogg, (1963).

It is to be noted that this conclusion is in contradiction to the multiple factor theory of Gray (1950). It is perhaps fitting to quote the dedication to his book "Pulmonary Ventilation and its Physiological Regulation". This reads: "To those physiologists whose contributions of imperishable data provoke perishable interpretations". One feels that Gray would indeed welcome discussion of the contradiction to his ideas which the present interpretation of ventilatory control in disease appears to imply.

Gray proposes the following multiple linear equation to quantitate the partial effects of arterial ( $H^+$ ) and  $PCO_2$  on ventilation (measured as the alveolar ventilation ratio, VR, being the ratio of the alveolar ventilation under stimulation to that at rest).

$$VR_{H \text{ } pCO_2} = 0.22H + 0.262 PCO_2 - 18.0$$

It is to be noted that Gray's equation is in terms of the alveolar ventilation ratio, whereas the results in Figure 43 are calculated on the basis of a constant minute volume of 10 litres/minute. In the patients with renal failure, ammonium chloride acidosis, bicarbonate alkalosis, and altitude acclimatisation, it seems not unreasonable to assume that the lungs were normal, and that the physiological dead space in these patients would be approximately similar in all. It would therefore follow that the alveolar ventilation would be roughly similar in all these subjects when the minute volume was constant at 10 litres/minute. Thus Gray's formula could be applied to these results.



This is done in Table 37, which gives the alveolar ventilation ratio predicted from the Gray equation for each of the acid base states discussed in Figure 43.

The bronchitic cases, however, undoubtedly do have an increase in the physiological dead space, and it is not reasonable to assume that a minute volume of 10 litres/minute in these patients will produce the same alveolar ventilation as that occurring in the subjects with normal lungs, at the same minute volume. The alveolar ventilation in the bronchitics will undoubtedly be less. It therefore follows that in fact these patients would require higher values of both arterial  $\text{PCO}_2$  and  $(\text{H}^+)$  in order to increase their alveolar ventilation to a level comparable to that in the other subjects in Figure 43. Therefore the deviation from the Gray equation will be even greater than that demonstrated in Table 37, at least for these subjects.

In fairness to Gray, it must be admitted that his conclusions were based on experimental data which did not include the severe degree of metabolic or respiratory disturbance covered by the present analysis (for example, his  $(\text{H}^+)$  range was 32 - 58 nanoMols/litre). The greater departure from his predictions in the respiratory acidosis is presumably merely a restatement of Scott's (1920) original observation. These patients do indeed breathe less for a given  $\text{PCO}_2$ ! Gray, in fact, did not consider any results from patients with respiratory acidosis in his review, but worked from the results of carbon dioxide inhalation studies in normal subjects.

## 5. The Effects of Hypoxia as a Ventilatory Stimulant:

As discussed in Chapter II, both the early work of Nielsen and Smith (1951) and the later work of the Oxford School, have shown that hypoxia interacts with hypercapnia in a normal subject by increasing the slope of a steady state carbon dioxide response curve. It therefore appears simple to compare the ventilatory stimulant action of hypoxia in the normal subject and the bronchitic patients by a comparison of slopes of the regression equations  $V = S_{CO_2} (PCO_2 - B_{CO_2})$ . There is one important provision, however, stemming from these previous studies - this concerns the accuracy with which the isoxic conditions must be maintained. This is highly relevant for the low oxygen condition, for Cunningham, Shaw, Lahiri and Lloyd (1961) demonstrated that the relationship between  $S_{CO_2}$  and  $PO_2$  of the isoxic line was hyperbolic, so that  $S_{CO_2}$  increased markedly as the  $PO_2$  fell towards 30 - 40 mm.Hg.

When the present results are examined from this point of view, the control of  $PO_2$  was found to be unsatisfactory in the studies on normal subjects. The criteria used were that the  $PO_2$  levels during an isoxic line, below 80 mm.Hg should be within  $\pm 5$  mm.Hg. These limits are derived from the studies of Falchuk, Lamb and Tenney (1966), on three normal subjects. Similarly, only five of the eight bronchitic subjects (numbers 9, 11, 12, 13 and 15) in the main experiments yielded lines controlled within these limits. The reason for this failure depended upon two things. The first was the inability to prevent breathing from the

atmosphere during the high ventilation rates encountered in hypoxic hypercapnic hyperventilation in normal subjects, when the pneumotachygraph was used to measure ventilation. The second factor was the inability of the blood gas  $PO_2$  measurements to provide the accuracy and rapidity in analysis required. Although one sample was taken after five minutes on a particular gas mixture, the result was not known for a further five minutes and adjustment of gas mixtures and a further trial unduly prolonged the most unpleasant part of the experiment for the subject. The analysis of alveolar (or end-tidal) gas as used by the Oxford workers and by Falchuk, Lamb and Tenney (1966) renders this control much easier, but such samples would have been useless in the bronchitic patients and therefore were not adopted for use in the normal subjects. With hindsight, this was the greatest technical error in these experiments.

In order, therefore, to obtain adequate data with which to compare the results in the bronchitic patients, the studies of Cunningham, Shaw, Lahiri and Lloyd (1961) and Falchuk, Lamb and Tenney (1966) have been used. Another problem then appears - that of a method of expressing the comparison between normal subjects and bronchitics which is not influenced by the depressed response to carbon dioxide which characterises the bronchitic. To avoid this problem, each slope ( $S_{CO_2}$ ) of the regression line under hypoxic conditions

was expressed as a ratio of the slope ( $S_{CO_2}$ ) in the same patients when the  $PO_2$  was over 100 mm.Hg. The results of this comparison are shown in Table 38. There is no significance in the difference ( $0.10 > P > 0.05$ ) between the mean values of the ratio for the normal subjects and the bronchitic patients in this Table. It follows, therefore, that this study does not support the suggestion that the patient with chronic respiratory failure has an increase in sensitivity to hypoxia as a respiratory stimulant. This problem, however, is of some considerable importance, in view of the common clinical problem of hypoventilation on oxygen which the bronchitic displays (Chapter II). It was particularly to examine this point that the subsidiary experiments (subjects 16 - 25) were planned. As described in the section on Methods (Chapter V), great care was taken to try and maintain isoxic conditions, particularly during the critical low  $PO_2$  levels, in these experiments.

A study of Figure 41, and Table 35, however, reveals a new problem. The Oxford concept of a common value of " $B_{CO_2}$ ", the intercept on the carbon dioxide axis, which is independent of  $PO_2$  of the isoxic line, is clearly not upheld in the results from these experiments. Statistically, in fact, only in cases 16, 23 and 24 does the value of  $B_{CO_2}$  for one of the two lines fall within two standard deviations of the other value of  $B_{CO_2}$ . This comparison of the values of  $S_{CO_2}$  alone, to compare the effects of hypoxia, is clearly no longer valid, and in order to overcome this difficulty, an alternative approach was devised.



The amount of the rise in arterial  $\text{PCO}_2$  necessary to double the resting ventilation, when the arterial  $\text{PO}_2$  is maintained at that found when breathing air (the "resting ventilation" condition), is expressed as a ratio of the rise in arterial  $\text{PCO}_2$  necessary to double the resting ventilation, when the arterial  $\text{PO}_2$  is over 100 mm.Hg. Thus in terms used in Figure 44, this "hypoxic index" of ventilatory control is:-

$$\text{Hypoxic index} = \frac{C - A}{B - A}$$

and is therefore a dimensionless quantity. The greater the effect of the hypoxia the greater the value of the index.

In order to allow of comparison with normal subjects, it is imperative that the level of arterial  $\text{PO}_2$  at the "resting ventilation" be defined when a value for the index is given. For the bronchitic subjects 9, 11, 12, 13, 15, 16, 17, 18, 19, 21, 22, 24 and 25, where the control of the  $\text{PO}_2$  levels at the low isoxic line is adequate, the results are given in Table 39, with appropriate levels of  $\text{PO}_2$ . For the normal subjects of Cunningham, Shaw, Lahiri and Lloyd (1961) and Falchuk, Lamb and Tenney (1966), the values of the "Hypoxic Index" are given for the various values of  $\text{PO}_2$  which were studied on the low isoxic lines.

Three comparisons are made between the values of the hypoxic index in the normal subjects and the bronchitic patients. In the first the comparison is between values of the index on the low  $\text{PO}_2$  line, between 50 and 69 mm.Hg (normal subjects 59-61, 58-66, 60-65, 60-65

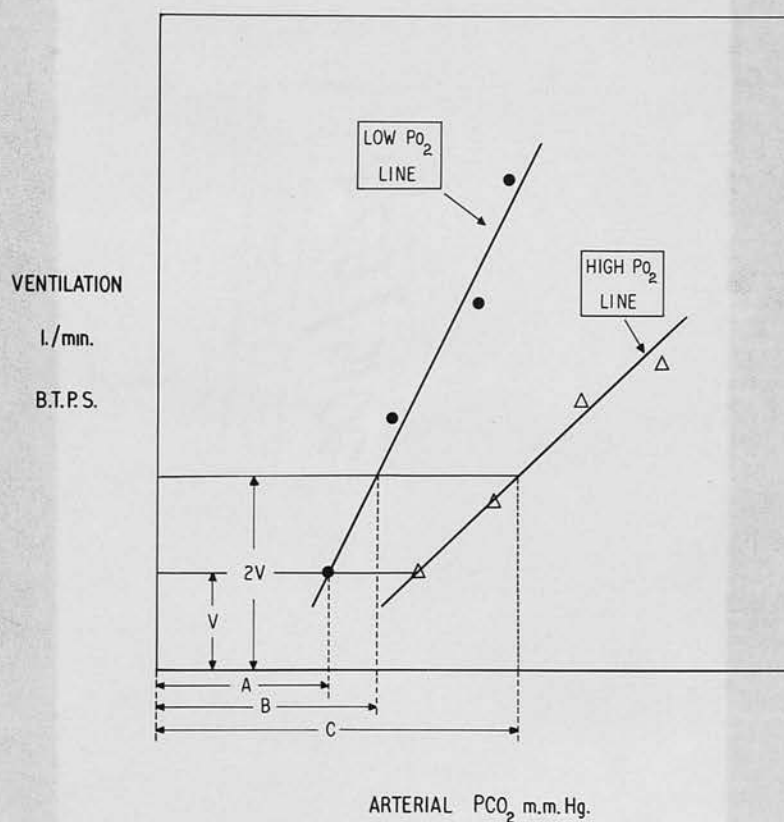


Figure 44

Diagram to explain the derivation of the "Hypoxic Index". For explanation see text.

60-65, and bronchitic patients 60-69, 54-66, 50-68 and 50-65 mm.Hg  $PO_2$ ). There is no significant difference ( $P > 0.10$ ) between the values of the hypoxic index in the normal subjects and bronchitic patients for this range of  $PO_2$  levels for the hypoxic line.

The second comparison was made at lower levels of  $PO_2$  between 47 - 59 mm.Hg (normal subjects 50-55, 50-55, 50-55, bronchitic patients 49-54, 47-59, 50-55, 50-55, 50-55, 50-55, 50-55, 50-55 mm.Hg  $PO_2$  for the low isoxic line). Again no significant difference ( $P > 0.10$ ) could be determined in the values of the index between normal subjects and bronchitic patients.

Finally, a comparison was made at the lowest level of  $PO_2$  studied for the isoxic line (normal subjects 41-49, 44-50, 40-45, 40-45, 40-45, bronchitic patients 39-39, 43-49, 40-53, 33-48 mm.Hg  $PO_2$  for the low isoxic line) The results here do show a significant difference between the mean values of the hypoxic index between the normal and bronchitic subjects ( $0.05 > P > 0.02$ ). The normal subjects had much greater values for the hypoxic index at these levels of hypoxia than did the normal bronchitic patients.

Thus once again these results on the extended series, including 13 patients with chronic respiratory failure, do not provide any evidence for an increased sensitivity to hypoxia in the bronchitic patient with respiratory failure.

## CHAPTER IX

### INSPIRATORY WORK : RESULTS

The measurement of inspiratory work can be considered in two categories, the work done on the lungs, and the total work done on the respiratory system during inspiration. The work done on the lungs is obtained by the pressure-volume traces of instantaneous tidal volume against the instantaneous pressure between the

## CHAPTER IX

### INSPIRATORY WORK : RESULTS

1 - 7 (normal) and cases 8 - 15 (bronchitis).

#### The Inspiratory Work Done on the Lungs

The values for inspiratory work on the lungs are presented as four values: EWT, the elastic work done in a single breath, VWT, the viscous work done in a single breath, REW, the rate of elastic work, and RW, the rate of viscous work. The mean values for these measurements, with one standard deviation, for each level of arterial  $PO_2$ ,  $PCO_2$  and  $(H^+)$  in each subject are given in Tables 6 to 21. In addition, values of the dynamic compliance for each period are also given, in litres BTPS/cm.  $H_2O$ . The units of work are kilogram metres expressed as kilogram metres/minute when rates of work are considered (kg.m./min). These units, although slightly large for the values involved here, are conventional for expressing the mechanical work of breathing.



## CHAPTER IX

### INSPIRATORY WORK : RESULTS

The measurement of inspiratory work can be considered in two categories, the work done on the lungs, and the total work done on the respiratory system during inspiration. The work done on the lungs is obtained from the pressure volume traces of instantaneous tidal volume against the instantaneous differential pressure between the mouth and the oesophagus as described in Chapters II and V. These measurements were only made in the main experiments on cases 1 - 7 (normal) and cases 8 - 15 (bronchitic).

#### 1. The Inspiratory Work Done on the Lungs:

The values for inspiratory work on the lungs are presented as four values: EWT, the elastic work done in a single breath, VWT, the viscous work done in a single breath, REW, the rate of elastic work, and RVW, the rate of viscous work. The mean values for these measurements, with one standard deviation, for each level of arterial  $PO_2$ ,  $PCO_2$  and  $(H^+)$  in each subject are given in Tables 6 to 21. In addition, values of the dynamic compliance for each period are also given, in litres BTPS/cm.H<sub>2</sub>O. The units of work are kilogram metres, expressed as kilogram metres/minute when rates of work are considered (kg.m./min). These units, although clumsily large for the values involved here, are conventional for expressing the mechanical work of breathing.

The rate of viscous work when breathing air ranged from 0.123 kg.m./min. to 0.355 kg.m./min. in the normal subjects with a mean value of 0.230 kg.m./min. In the bronchitic patients the rate of viscous work when breathing air ranged from 0.298 kg.m./min. to 0.780 kg.m./min. with a mean value of 0.461 kg.m./min.

The rate of elastic work done on the lungs ranged between 0.139 kg.m./min. and 0.314 kg.m./min with a mean of 0.217 kg.m./min. in the normal subjects. This mean value is very similar to the mean value of viscous work rate in these subjects implying that, at least when breathing air, these normal subjects divided the work rate on the lungs equally between viscous and elastic work.

For the bronchitic subjects the rate of elastic work (REW) done on the lungs ranged from 0.206 kg.m./min. to 0.395 kg.m./min, with a mean of 0.286 kg.m./min. This is considerably less than the mean rate of viscous work in these subjects, when breathing air, and would suggest that an increased pulmonary resistance (airways resistance + lung tissue resistance) is more important than changes in dynamic compliance in the disordered mechanical function of the bronchitic, for the differences in the rate of elastic work between the two groups are very small.

In this regard, of course, the manner in which the minute volume of ventilation was distributed between the tidal volume and respiratory frequency is of some importance. The mean respiratory

1.

frequency in the normal subjects was 19 breaths/minute (range 16.4 to 21.1) when breathing air. This compares with values of 13.1 to 28.5 breaths/minute (mean 22.0) in the bronchitic cases. The mean tidal volume, when breathing air, was correspondingly lower in the bronchitic cases (mean 0.403 litres BTPS, range 0.290 to 0.524) versus a mean value in the normal cases of 0.491 litres BTPS (range 0.460 to 0.612). These give mean values of minute volume which are similar, at 9.26 litres/min. BTPS in the normal subjects and 8.44 litres/min. BTPS in the bronchitic patients.

2. The Inspiratory Work Done on the Respiratory System:

As discussed in Chapters III and V, this involves the work done on the chest wall, in addition to the work done on the lungs. As shown in Chapter V, the method of pressure breathing, which was used to measure the total thoracic compliance, produces results which are not significantly different from zero, for the values of chest wall compliance in the bronchitic, although the values are valid in the normal subjects. It therefore follows that values for the total thoracic compliance in the bronchitic are at best approximations. The present results of total respiratory work cannot be regarded as accurate measurements, therefore, in the bronchitic subjects.

One other problem arises. If the patient takes a tidal breath from an end tidal volume which is at the functional residual capacity (as in A of Figure 45), the elastic work done on the whole thoracic

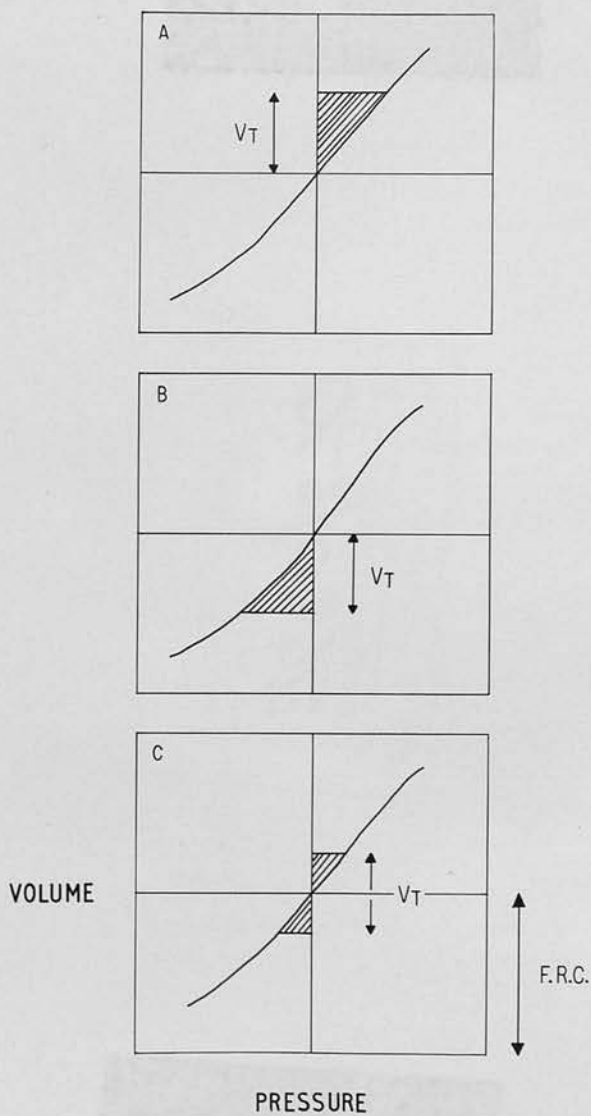


Figure 45

The effect of variation in position of the end tidal point on the area to be included in the calculation of the total elastic inspiratory work,  $V_T$  = tidal volume, F.R.C. = functional residual capacity. For further explanation, see text.



system is equal to the area shaded in A, for the total thoracic compliance line passes through the origin, as the inspiratory and expiratory musculature are both relaxed, with zero trans-thoracic pressure at the functional residual volume.

However, if the patient inspires to the functional residual volume, from an end tidal point well below this level (as in B of Figure 45), then the work done on inspiration will be equal to the area shaded in B. This work, however, will in fact have been done in the expiratory phase of the previous cycle, by lowering the end tidal point below the functional residual capacity. Thus the inspiratory muscles will not be required to contract actively to overcome elastic forces during this inspiration.

Finally, if the subject starts an inspiration from a point below the functional residual capacity and finishes above that level, the work done against elastic forces is that shown in C of Figure 45. The purpose of this digression is to emphasise that the position of the end tidal point greatly influences the method of measuring the inspiratory work. Simple geometry can demonstrate that the area shaded in **B**, for a given constant tidal volume, is much less than that in A or **B**. Unfortunately, the method of measuring tidal volume from an integrated pneumotachygraph record was not suited to determination of the true end tidal point in relationship to the level of the functional residual capacity, due to baseline drift in the integrator, over time. This problem was not appreciated until the experiments were completed.

However, it is possible to obtain some approximate idea as to the end tidal point in any loop as follows. This approach requires two assumptions, both of which appear reasonable, but cannot be fully substantiated. The first is that the lung compliance line is approximately linear over the range of tidal volumes considered in these experiments. If this were true, of course, then the values of compliance for each period in Tables 6 - 21 would be the same for each patient. The deviation from equality shown by these figures, therefore, indicates the validity of this assumption.

The second assumption is that this compliance line will always pass through the point on the pressure volume (Campbell) plot which represents conditions at the functional residual capacity. Furthermore, it is assumed that the oesophageal pressures, taken in the sitting position during quiet breathing of air in the first period, will measure the absolute mean intrapleural pressure at the functional residual volume. This is again an approximation to the truth, but one that is not intrinsically improbable.

If these conditions be granted then by using the measured compliance line and the measured mean oesophageal pressure at the end tidal point, it is possible to fix the range of any tidal volume on the pressure volume plot with reference to the functional residual capacity. This was done geometrically by using the compliance line as a Cartesian co-ordinate, whose origin was the elusive end tidal point. If the Cartesian

line had to pass through a fixed point (the pressure volume point of the functional residual capacity), the end tidal point was determined on the volume axis by the known pressure at that point. Again it must be stressed that this method was used as an approximation, for the precision can be no greater than that of the assumptions on which the method is based. If the problem of the end tidal position had been appreciated, attempts to determine this continually and accurately, possibly by use of a box-bag apparatus to determine ventilation, might have been made. The procedure in a *bronchitic* subject is illustrated in Figure 46.

### 3. Total Elastic Work of Inspiration:

From use of the compliance line of the total respiratory system, it is possible to calculate the work done on a pressure volume diagram, in terms of the elastic work at any tidal volume. By reference to Figure 47, it is apparent that any tidal volume, shown as the limits of inspiration and expiration on a lung compliance line, is divided into two parts, A litres and B litres, so that:

$$V_T = A + B$$

If the angle  $\alpha$  is that made by the total thoracic compliance line on the pressure axis, it follows that  $\cotangent \alpha = \text{Total Thoracic Compliance}$ , when corrected for the scaling factors of the graph. By simple geometry the area representing total elastic inspiratory work (TEW) on the thorax is:

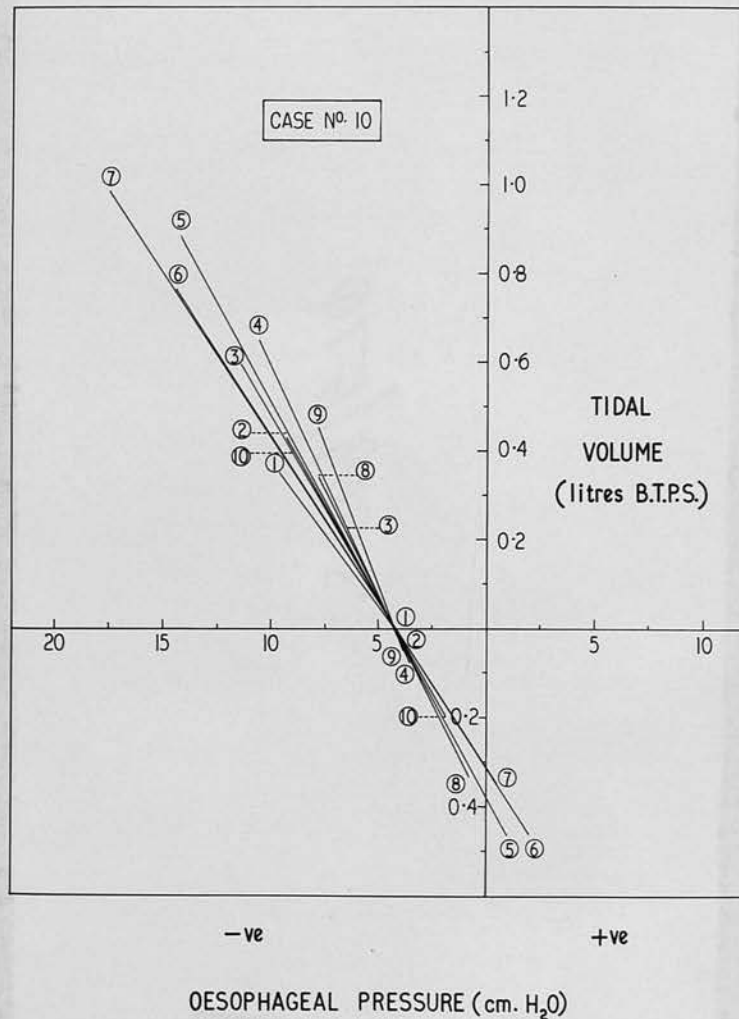


Figure 46

The method of determining the end tidal point from the pressure volume diagrams of the lung. The reference point, at F.R.C. as volume, is taken as the mean oesophageal pressure at the mean end tidal point when breathing air in the first period. The mean linear compliance lines for each period are drawn to pass through this point, and the mean oesophageal pressure at the mean end tidal point in these different periods is used to determine the end tidal point on the relevant compliance line, and thence on the volume axis, with reference to the F.R.C. Actual data from Case 10. The numbers mark the upper and lower limits of each mean tidal volume for each period of the study.



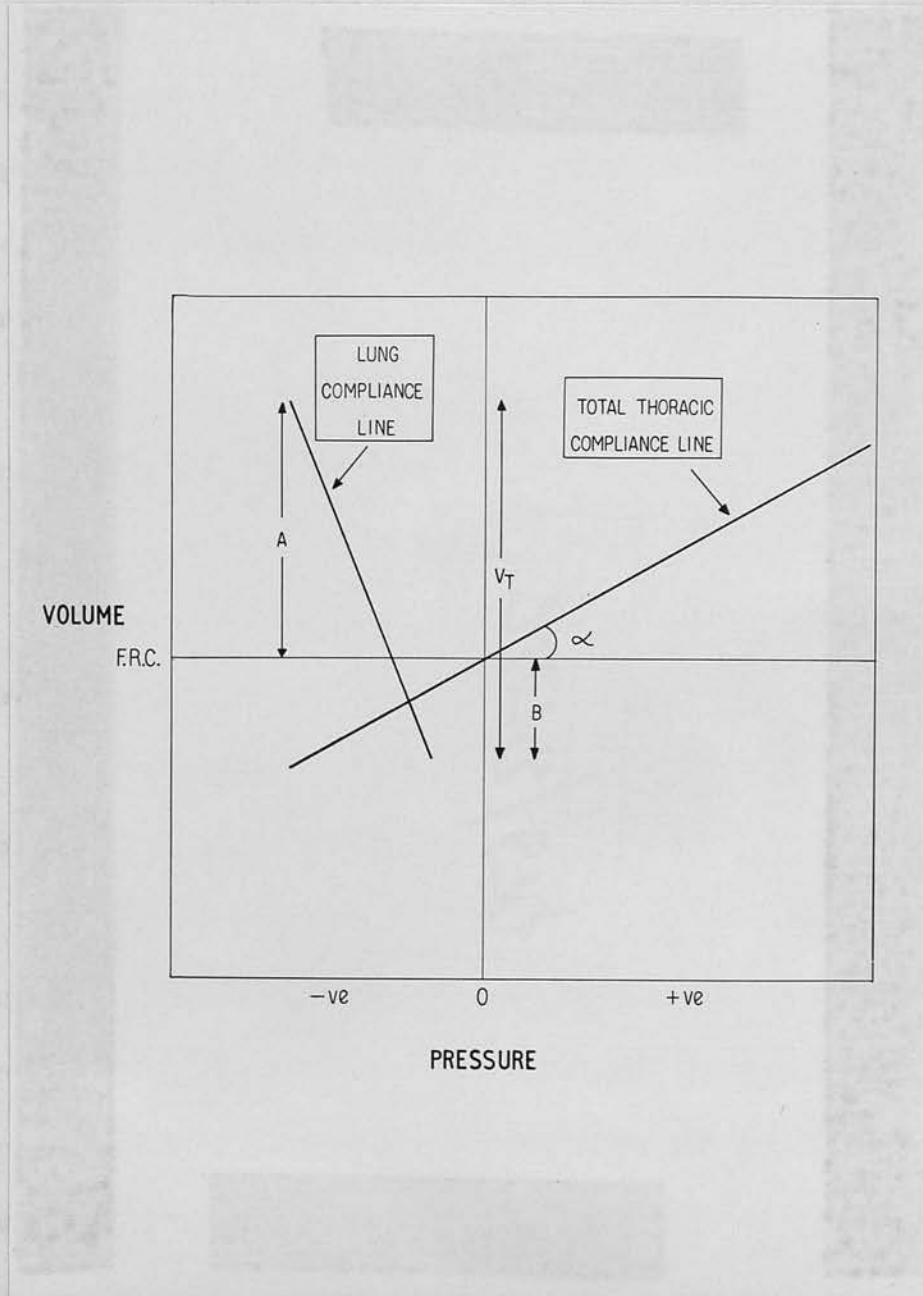


Figure 47

The method of calculation of the total elastic inspiratory tidal work, on the lungs and total thorax. For explanation, see text.

$$TEW = (A^2 + B^2) \cot \alpha$$

By use of this equation, therefore, values of TEW are calculated for each period in each subject, using the mean tidal volume during that period. These values, when multiplied by the mean respiratory frequency, become the rate of total elastic work done in inspiration (RTEW). This value RTEW is given for each period for each subject, in kgm/min. in Tables 6 to 21.

#### 4. Total Inspiratory Work:

This is made up of the rate of total elastic work done on the thorax during inspiration (RTEW) and in addition the rate of viscous work done on the lungs (RVW). This value is given in Tables 6 to 21 for each period, and each subject. It will be apparent that the inspiratory work also must include some component of viscous work done on the thoracic cage, but this cannot be measured in the conscious, non-paralysed subject who is breathing spontaneously. It is not therefore included in these calculations. Similarly, any work done on the abdominal contents during inspiration is likewise not available for measurement in these studies.

It must be emphasised that the calculation of elastic work done on the whole respiratory system is only calculated for the mean tidal volume of each period, and thus the standard deviation is not obtained.

5. Values of Total Inspiratory Work when Breathing Air:

From the data in Tables 6 to 21, it is seen that the rate of total inspiratory work when breathing air, in the normal subjects (cases 1 to 7, excluding case 5 with insufficient data, and case 3 who was not studied when breathing air) ranged from 0.416 kg.m./min. to 0.642 kg.m./min. with a mean of 0.482 kg.m./min. When this is expressed for each subject as the rate of total inspiratory work for each litre/min. of resting ventilation, when breathing air, the values range from 0.043 kg.m./litre to 0.073 kg.m./litre, with a mean value of 0.054 kg.m./litre.

In the bronchitic subjects, when breathing air (cases 8 to 15), the rate of total inspiratory work ranged from 0.480 to 1.219 kg.m./min., with a mean of 0.740 kg.m./min. Again expressing these results as the rate of total inspiratory work per litre of resting ventilation (when breathing air) the values in these cases ranged between 0.072 kg.m./litre to 0.110 kg.m./litre, with a mean value of 0.086 kg.m./litre. Thus these bronchitic patients were expending considerably more energy than the normal subjects in ventilating their lungs at rest.

## CHAPTER X

### INSPIRATORY WORK: DISCUSSION

The measurements of inspiratory work presented in Chapter IX are based upon two experimental procedures. In the one (the measurement of the viscous work done on the lungs), the viscosity of the measurement depends principally upon the records of instantaneous tidal volume and the aerodynamic pressure difference. Many methods have been used in each patient, and the method is well established provided that the patient is sitting upright. The other measurements concern the addition of inspiratory viscous work (from the pressure-volume measurements) to calculations based on measurements of total thoracic compliance derived from the pressure-volume measurements. These measurements are considerably more prone to error. Not only is this a random error which can be minimized by repetition of measurements, but, as discussed in Chapters II and VI, there seems a possibility that the total thoracic compliance measurements may be subject to an unknown systematic error, particularly in the hydrothoracic patients. For these reasons, therefore, much of the discussion in this chapter will centre on the measurements of viscous work done on the lungs, for this important quantity is probably measured in these present experiments by methods which are less likely to suffer from the introduction of unknown systematic errors. This is not to diminish the importance of the total inspiratory work, but is in deference



## CHAPTER X

### INSPIRATORY WORK: DISCUSSION

The measurements of inspiratory work presented in Chapter IX are based upon two experimental procedures. In the one (the measurement of the viscous work done on the lungs), the veracity of the measurements depends principally upon the records of instantaneous tidal volume and the oesophageal to mouth instantaneous pressure difference. Many measurements are made in each patient, and the method is well established provided that the patient is sitting upright. The other measurements concern the addition of inspiratory viscous work (from the pressure volume measurements) to calculations based on measurements of total thoracic compliance derived from the pressure breathing experiments. These measurements are considerably more prone to error. Not only is this a random error which can be minimised by repetition of measurements, but, as discussed in Chapters II and VI, there seems a possibility that the total thoracic compliance measurements may be subject to an unknown systematic error, particularly in the bronchitic patients. For these reasons, therefore, much of the discussion in this chapter will centre on the measurements of viscous work done on the lungs, for this important quantity is probably measured in these present experiments by methods which are less likely to suffer from the introduction of unknown systematic errors. This is not to diminish the importance of the total inspiratory work, but is in deference

to a sober appraisal of the extreme difficulties of making such measurements in the bronchitic, and an awareness of the dangers of over-interpretation of faulty data.

# 1. The Theoretical Estimation of the Mechanical Work of Breathing Done on the Lungs:

As Otis (1964) points out, following Rohrer's (1925) analysis, a simplified form of the equation of motion for the respiratory system is:

$$P_{app.} = \frac{1}{CL} V + k_1 \dot{V} + k_2 \dot{V}^2 \quad (1)$$

where  $P_{app.}$  = Applied pressure differential,  $CL$  = compliance,  $V$  = displacement from relaxation volume,  $\dot{V}$  = rate of change of volume, and  $k_1$  and  $k_2$  are constants. If the breathing pattern is sinusoidal, so that

$$\dot{V} = a \sin bt \quad (2)$$

where  $\frac{b}{2\pi} = f$  = breathing frequency and  $a$  = peak flow in the cycle,

then Otis goes on to show that:

$$W_{insp.} = \frac{1}{2CL} V_T^2 + k_1 \frac{\pi^2}{4} \cdot V_T^2 + k_2 \frac{2\pi^2}{3} \cdot f^2 \cdot V_T^3 \quad (3)$$

where  $W_{insp.}$  = the work of one inspiratory cycle.

In this equation (3):

$$\frac{1}{2CL} \cdot V_T^2 = 100 \text{ EWT} \quad (4)$$

where EWT is the elastic work done on the lungs in one tidal breath (Chapter IX). The factor of 100 arises as  $V_T$  is expressed in litres and  $CL$  in litres/cm. $H_2O$ , and EWT is in kg.m. It must be pointed out that the general form of the equation for inspiratory work (equation 3) was applied by Otis to the work done on the whole respiratory system.

Nonetheless, provided that the sinusoidal displacement is considered as applying to the lungs and provided that CL is the pulmonary compliance the equation can be applied to the work done on the lungs during a tidal breath. It must follow that:

$$W_{\text{insp.}} = EWT + VWT \quad (5)$$

where again, VWT is the viscous work in a tidal breath. Thus, equation (3), by substitution of (4) and expressing the work in kg.m. becomes:

$$VWT = k_1 \cdot \frac{\pi^2}{400} f^2 \cdot V_T^2 + k_2 \frac{2\pi^2}{300} V_T^3 \quad (6)$$

In this equation (6),  $k_1$  will have the dimensions of cm.H<sub>2</sub>O litres/minute, and  $k_2$  will have the dimensions of cm.H<sub>2</sub>O/(litres/min.)<sup>2</sup>. As Otis states, these coefficients were originally considered to relate to the laminar and turbulent components of resistance to air flow, but "this interpretation is probably too simple and it now seems wiser to regard them as empirical constants".

By multiplying equation (3) by  $f$ , the frequency of breathing, the equation for the rate of inspiratory work ( $\dot{W}$ ) becomes:

$$\dot{W} = \frac{1}{2CLf} \cdot \dot{V}_E^2 + k_1 \frac{\pi^2}{400} \dot{V}_E^2 + k_2 \frac{2\pi^2}{300} \dot{V}_E^3 \quad (7)$$

Again, REW (the rate of elastic work on the lungs) is equal to:

$$\frac{1}{2CLf} \dot{V}_E^2 \text{ when the units are corrected, and this equation reduces}$$

to:

$$RVW = k_1 \frac{\pi^2}{400} \cdot \dot{V}_E^2 + k_2 \frac{2\pi^2}{300} \cdot \dot{V}_E^3 \quad (8)$$

where RVW is expressed in kg.m./min. and  $\dot{V}_E$  in litres/min.

If the rate of breathing were a constant, then values of  $k_1$  and  $k_2$  in equations (6) and (8) would be the same.

## 2. The Validity of These Estimates of the Mechanical Work in Case 7:

These estimates were analysed in detail when applied to the results of one normal subject (Case 7). The curve fitting and plotting of experimental data and the derived curves was carried out on the Elliott 803 computer, for a very considerable computational problem was involved with 173 experimentally determined points.

The first approach was to apply the computer plotting programme to the relationships between the total work done on the lung in inspiration, during one tidal breath (EWT and VWT) and the tidal volume ( $V_T$ ). The plot is shown in Figure 48. The relationships between the rate of inspiratory work (REW and RVW) and the minute volume for Case 7 is shown in Figure 49.

From the foregoing discussion, it is apparent that equation (2) reduces to equation (6), a simpler form in the same variables, and involving the same constants  $k_1$  and  $k_2$ . This form of equation was therefore fitted to the data, the equation being:

$$VWT = 0.00057 + 0.0996 \left( \frac{\pi^2}{400} \left( \frac{300}{T} \right) V_T^2 \right) - 0.000427 \left( \frac{2\pi^2}{300} \left( \frac{300}{T} \right)^2 V_T^3 \right) \quad (9)$$

when the regression line is not forced to pass through zero. This equation therefore produces values of  $k_1$  of  $0.0996 \pm 0.0082$  cm.H<sub>2</sub>O/litre/min., and a negative value of  $k_2$  of  $-0.000427 \pm 0.000058$  cm.H<sub>2</sub>O/(litre/min.)<sup>2</sup> for in this equation (9), T = no. of 1/5th sec. pulses in each



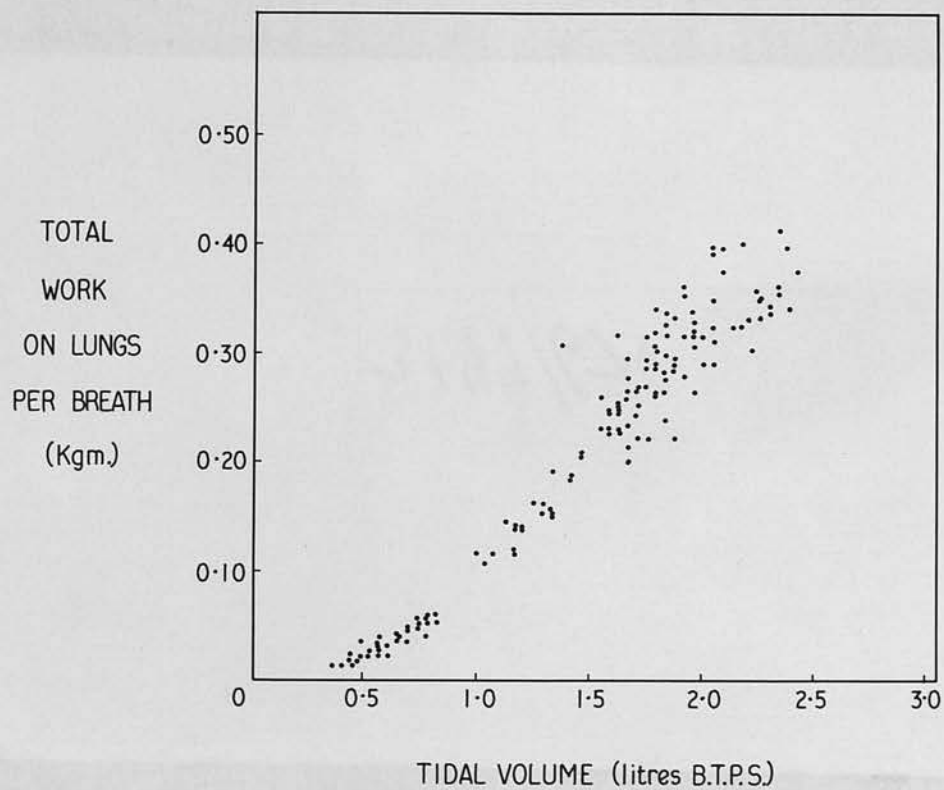


Figure 48

Inspiratory work on the lung (VWT and EWT) in each breath, as a function of the tidal volume of that breath. Data from Case 7.

complete breath,  $V_T$  = tidal volume in litres, and  $V_{WT}$  = viscous work of breathing done on the lungs in one breath, in kg.m.

The values of  $k_1$  and  $k_2$  are both highly significant ( $p < 0.001$ ) and both are significantly different from zero. This equation, when fitted

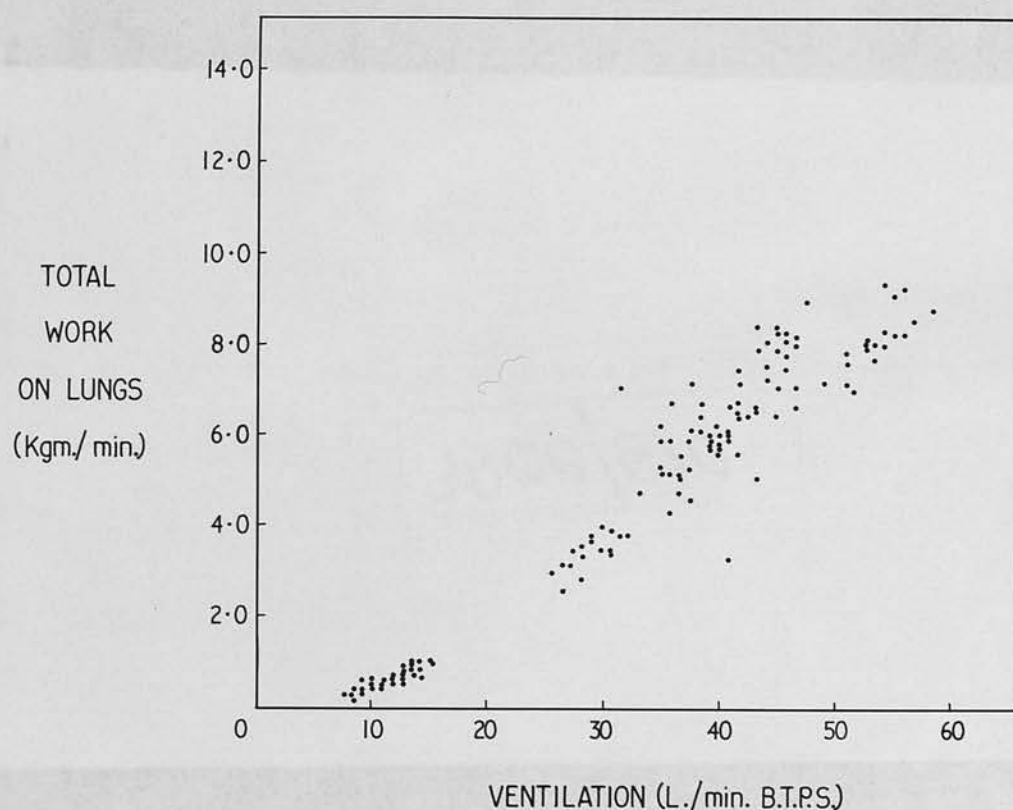


Figure 49

The rate of inspiratory work on the lung (RVW and REW) as a function of the minute volume. Data from Case 7.

complete breath,  $V_T$  = tidal volume in litres, and VWT = viscous work of breathing done on the lungs in one breath, in kg.m.

The values of  $k_1$  and  $k_2$  are both highly significant ( $p < 0.001$ ) and both are significantly different from zero. This equation, when fitted to the data, produces a reduction of 81.23% in the mean square deviation about the mean, or an efficiency of regression of 81.23% for 171 degrees of freedom.

However, on the soundest of theoretical grounds, namely that no work is done if no breathing occurs, or alternatively the tidal volume is zero, the line relating inspiratory viscous work and tidal volume must, in fact, pass through the origin. The programme was therefore run again, with the same data from Case 7, with the proviso that the line must be forced through the origin. This results in the equation:

$$\text{VWT} = 0.00012 + 0.1007 \left( \frac{\pi^2}{400} \left( \frac{300}{T} \right) V_T^2 \right) - 0.000434 \left( \frac{2\pi^2}{300} \left( \frac{300}{T} \right)^2 V_T^3 \right) \quad (10)$$

Again, VWT = viscous work of a tidal breath in kg.m.,  $T$  = number of 1/5th pulses in each single breath, and  $V_T$  = tidal volume in litres. This equation therefore yields values of  $k_1$  of  $0.1007 \pm 0.0055$  cm.H<sub>2</sub>O/litre/min., and  $k_2$  of  $-0.000434 \pm 0.000044$  cm.H<sub>2</sub>O/(litre/min)<sup>2</sup>. Again these values are highly significant ( $p > 0.001$ ), but this time the intercept value (0.00012 kg.m.) is not significantly different from zero. This equation will account for 81.22% of the reduction in the mean square deviation about the mean, for 172 degrees of freedom (note that the regression "gains" an extra value, of EWT = 0,  $V_T$  = 0, by the condition that the line must pass through the origin).

It will be obvious that both these equations produce a negative value for the cubic coefficient,  $k_2$ , in  $\text{cm.H}_2\text{O}/(\text{litre}/\text{min})^2$ . On the face of it, this coefficient is highly significant, but in fact this is a rather spurious significance, for the model of the equation fitted expressed that a cubic term was to be included. The necessity for a further term in the equation, however, beyond the second power of  $V_T$  is shown by the fact that this equation:

$$\text{VWT} = 0.0057 + 0.0478 \left( \frac{\pi^2}{400} \left( \frac{300}{T} \right) \right) V_T^2 \quad (11)$$

can be fitted to the data, with, however, only a reduction of mean square deviation about the mean of 70.77%, when the line is forced through the origin. In this equation in  $k_1$  the value of  $k_1$  is highly significant ( $p < 0.001$ ) with a value of  $0.0478 \pm 0.00114 \text{ cm.H}_2\text{O}/\text{litre}/\text{min}$ . From these calculations, therefore, it is apparent that equation (10) is a better fit to the data.

However, of more importance in the present study is the relationship between the rate of viscous work done on the lungs and the minute volume of ventilation. Here, the equation for Case 7, without forcing through the origin is:

$$\text{RVW} = 0.00569 + 0.1001 \left( \frac{\pi^2}{400} \right) \dot{V}_E^2 - 0.00043 \left( \frac{2\pi^2}{300} \right) \dot{V}_E^3 \quad (12)$$

with values of  $k_1$  of  $0.1001 \pm 0.0082 \text{ cm.H}_2\text{O}/\text{litre}/\text{min}$ ., and of  $k_2$  of  $-0.00043 \pm 0.000058 \text{ cm.H}_2\text{O}/(\text{litre}/\text{min})^2$  which are both highly significant ( $p < 0.001$ ). This equation accounts for 81.91% of the mean square deviation about the mean.



The same relationship, calculated for the condition where the line is forced through the origin, gives the equation:

$$RVW = 0.00128 + 0.1005 \left( \frac{\pi^2}{400} \right) \dot{V}_E - 0.00043 \left( \frac{2\pi^2}{300} \right) \dot{V}_E^3 \quad (13)$$

Here the values of  $k_1$  are  $0.1005 \pm 0.00557$  cm.H<sub>2</sub>O/litre/min., and  $k_2 = 0.00043 \pm 0.000045$  cm.H<sub>2</sub>O/(litre/min.)<sup>2</sup>, again both being highly significant ( $p < 0.001$ ). This equation has exactly the same reduction in mean square deviation about the mean of 81.91% as that found by equation (12).

The pictorial fit of this equation to the data is shown in Figure 56, where RVW is plotted against  $\dot{V}_E$  and the calculated line included, when passing through the origin (equation 13). The cubic form of the equation is apparent. It must be emphasised that the wide scatter of data in this Figure indicates the difficulties of measuring the appropriate area of "viscous respiratory work", which depends not only upon following the serpiginous outline of the inspiratory pressure volume plot, but also upon the difficulties of defining the "top" and "bottom" points of the loop, in order to define the compliance line, for this, of course, is the other boundary of the appropriate area.

### 3. The Relationship Between the Rate of Viscous Work and the Minute Volume in All Cases:

After reviewing the preliminary computations described in detail above for Case 7, it was decided to fit the equation (8) to the data from all the 15 cases. The results are given in Table 40, and the Figures

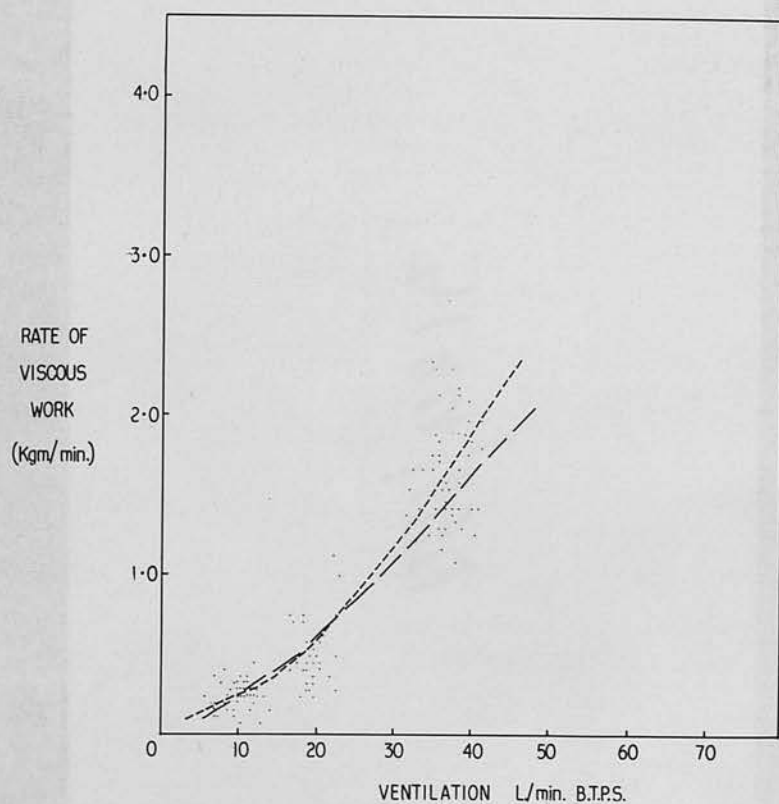


Figure 50

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from case 1.

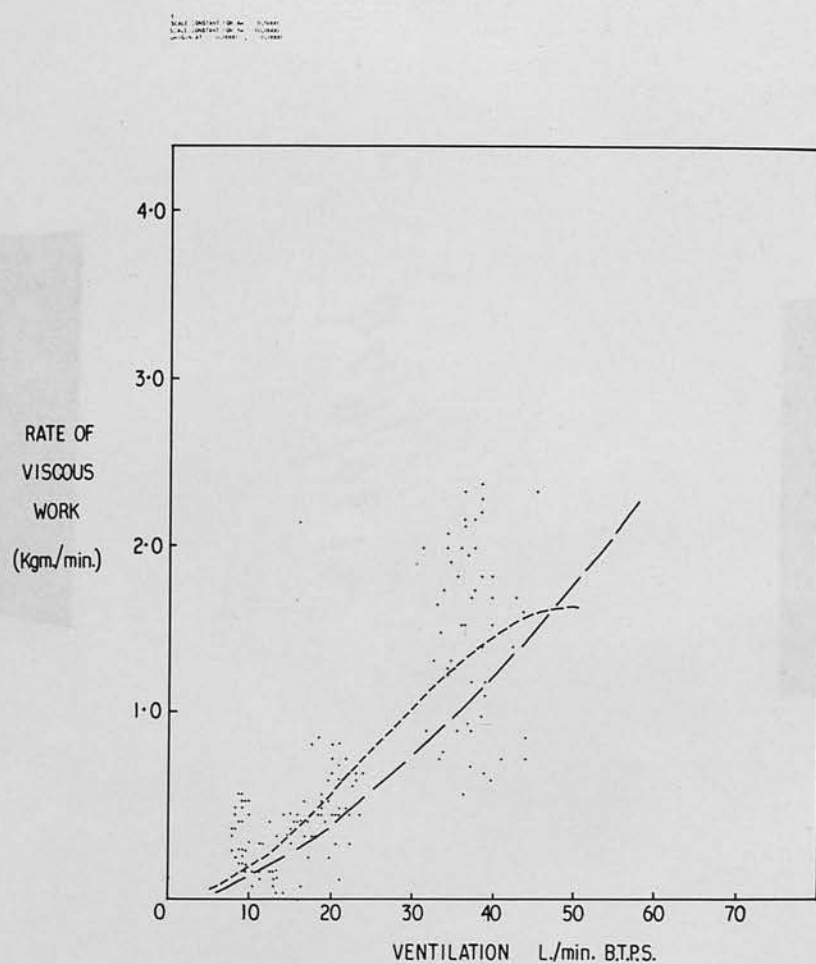


Figure 51

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 2.

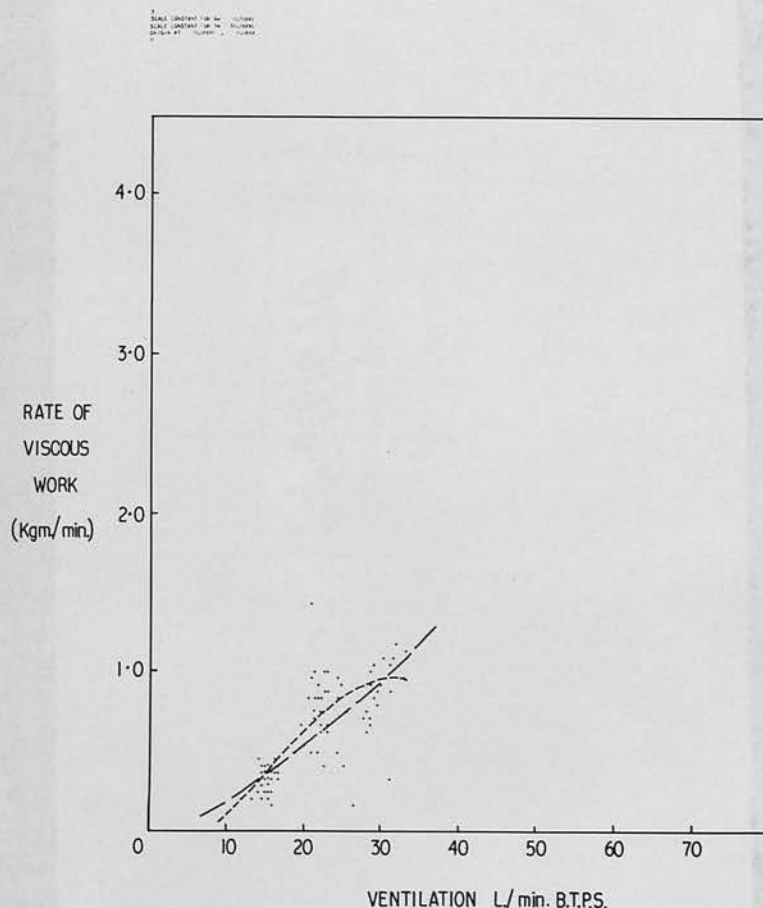


Figure 52

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 3.



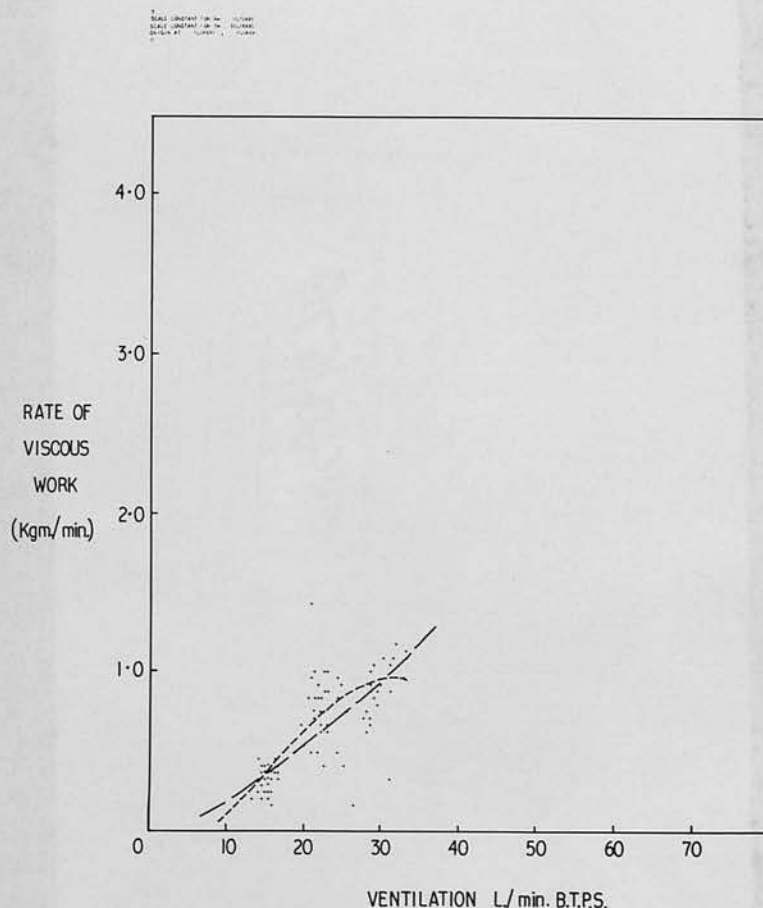


Figure 52

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 3.

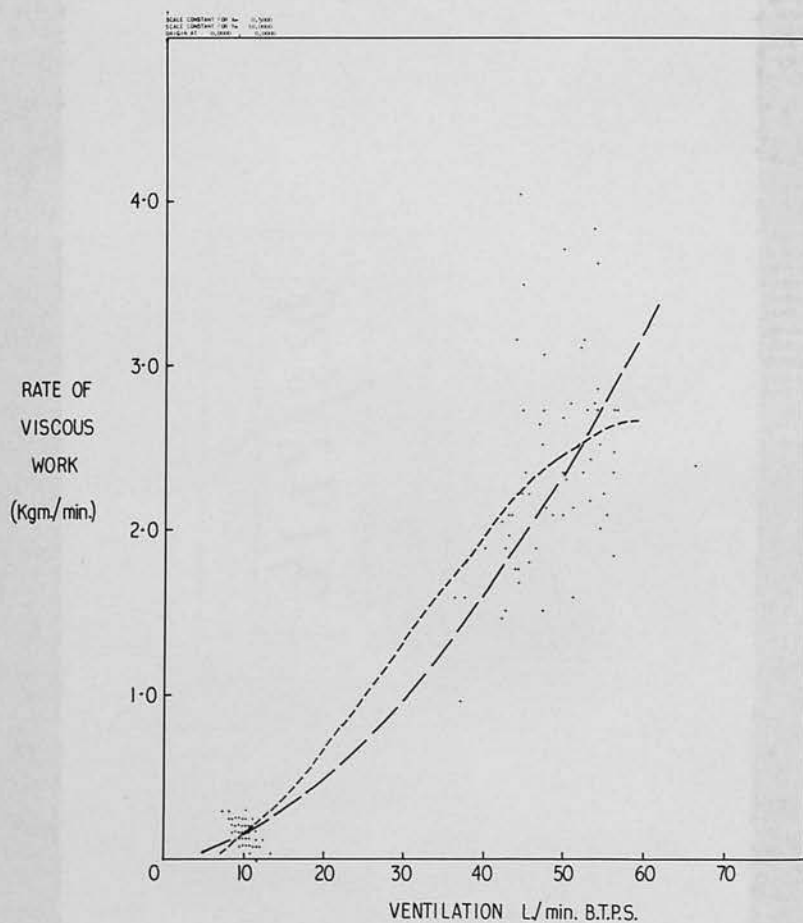


Figure 53

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $V_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 4.

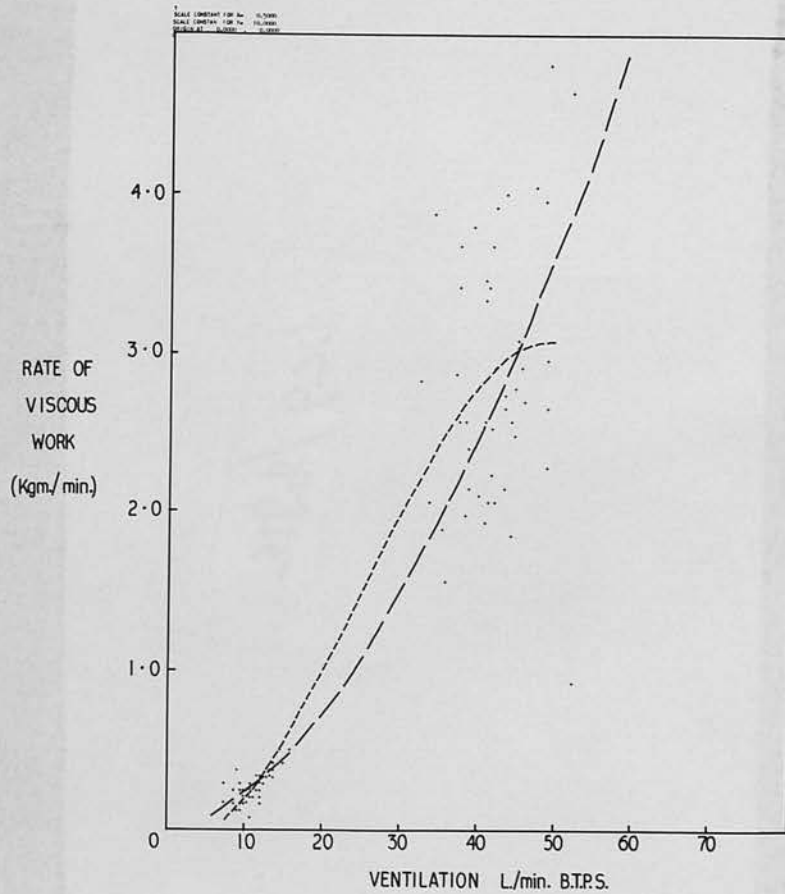


Figure 54

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 5.

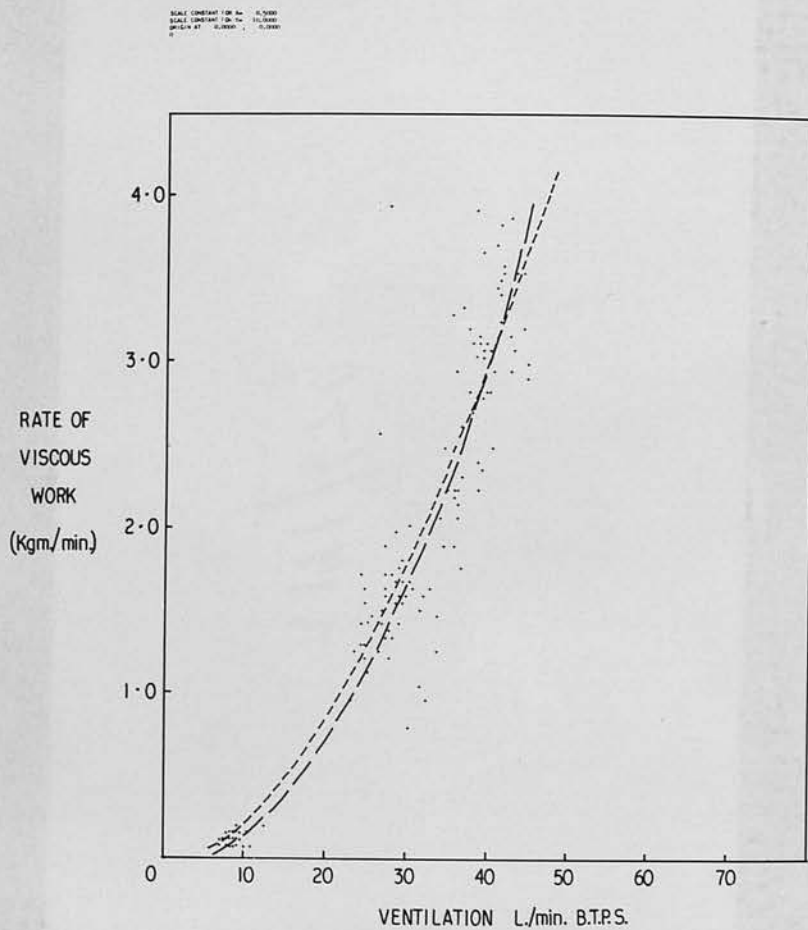
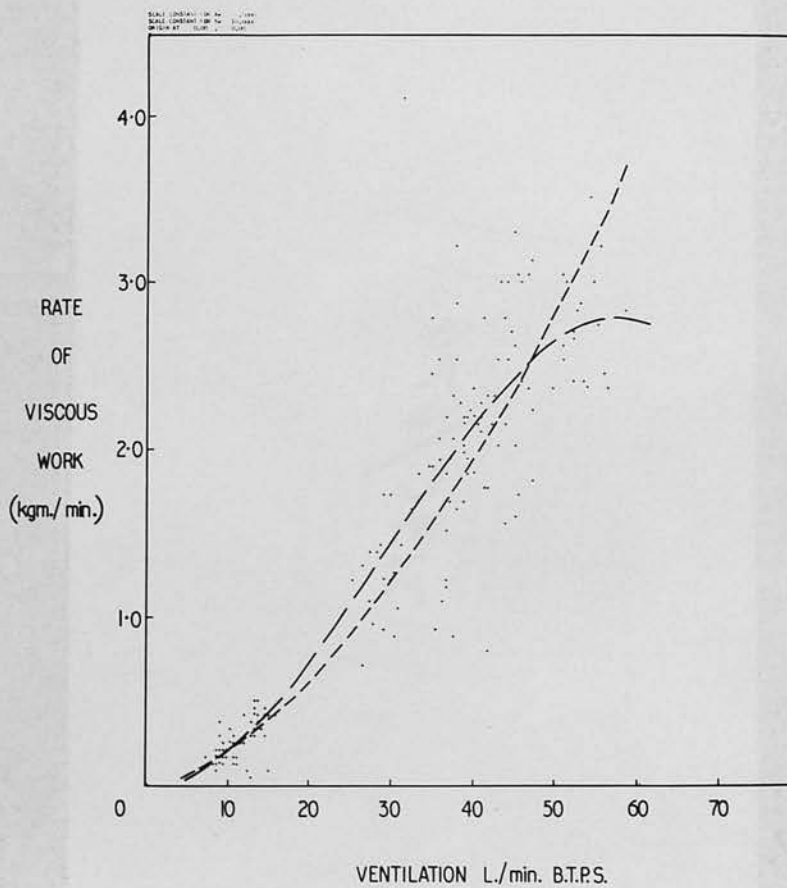


Figure 55

The relationships between the rate of viscous work on the lung ( $\dot{V}_E$ ) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 6.





**Figure 56**

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 7.

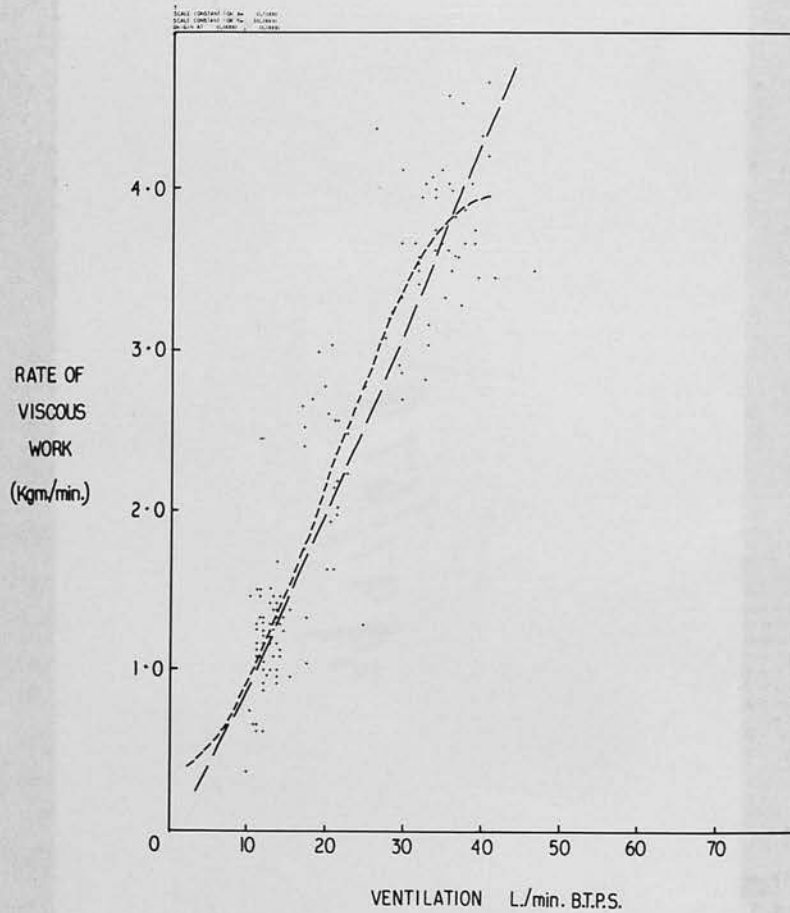


Figure 57

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 8.

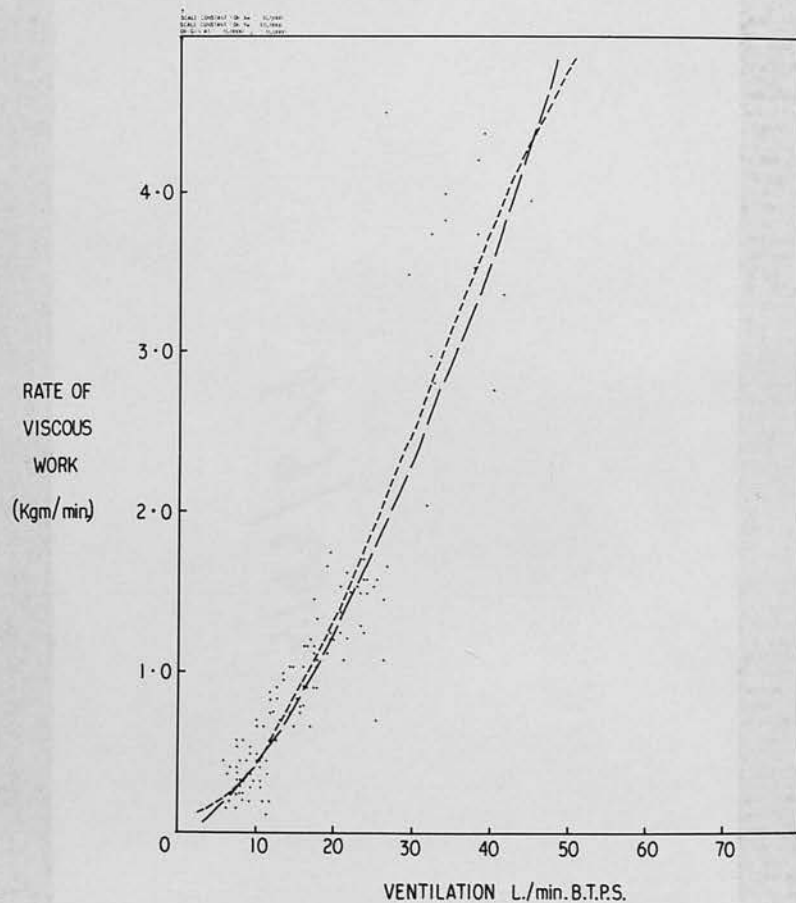


Figure 58

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $V_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 9.

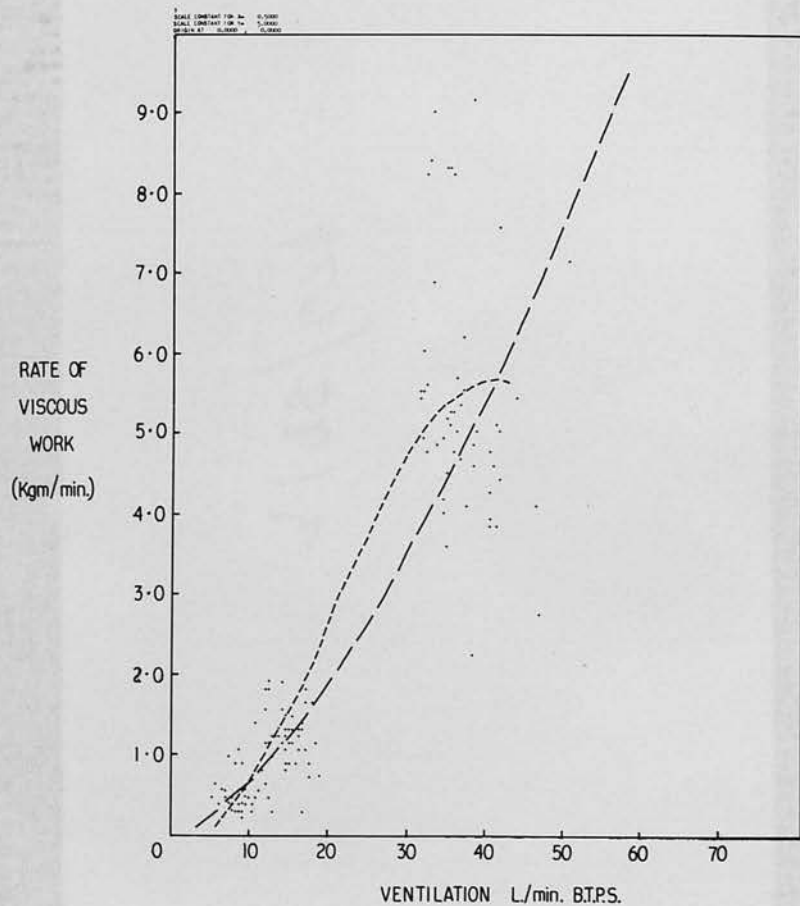


Figure 59

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $V_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 10.



SCALE CONSTANT FOR RVW  
SCALE CONSTANT FOR  $\dot{V}_E$   
SLOPE AT  $\dot{V}_E = 10$  L/min. B.T.P.S.

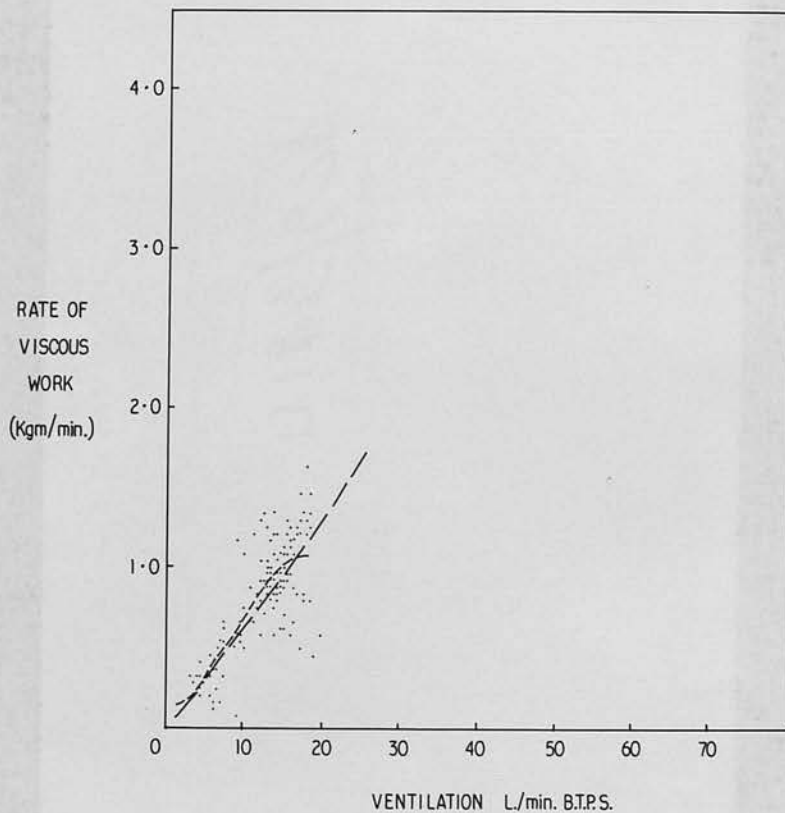


Figure 60

The relationship between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 11.

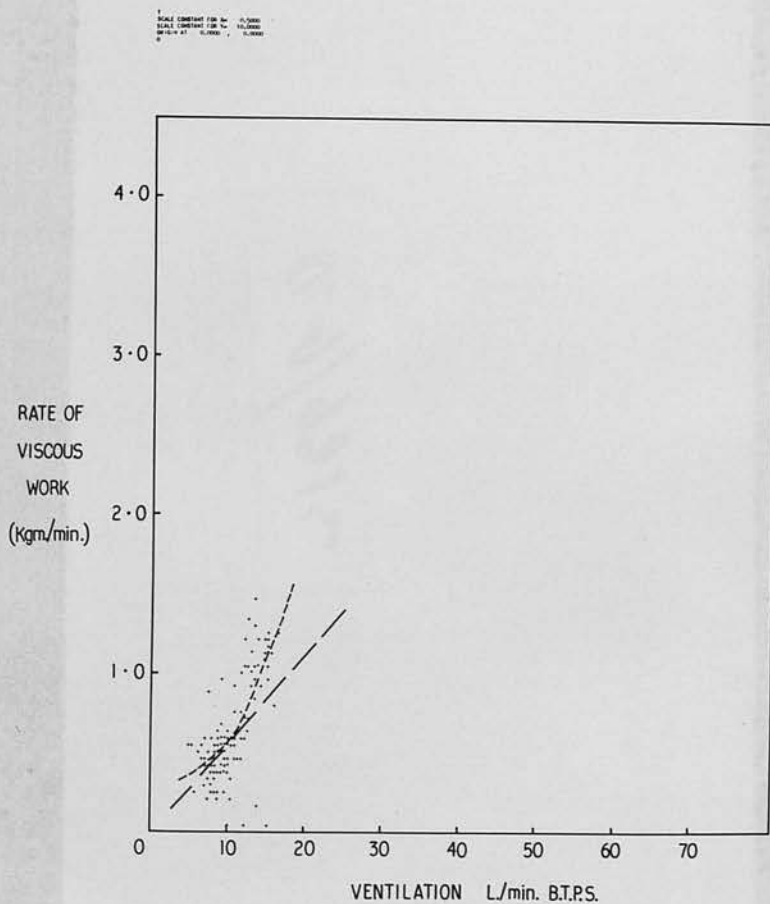


Figure 61

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 12.

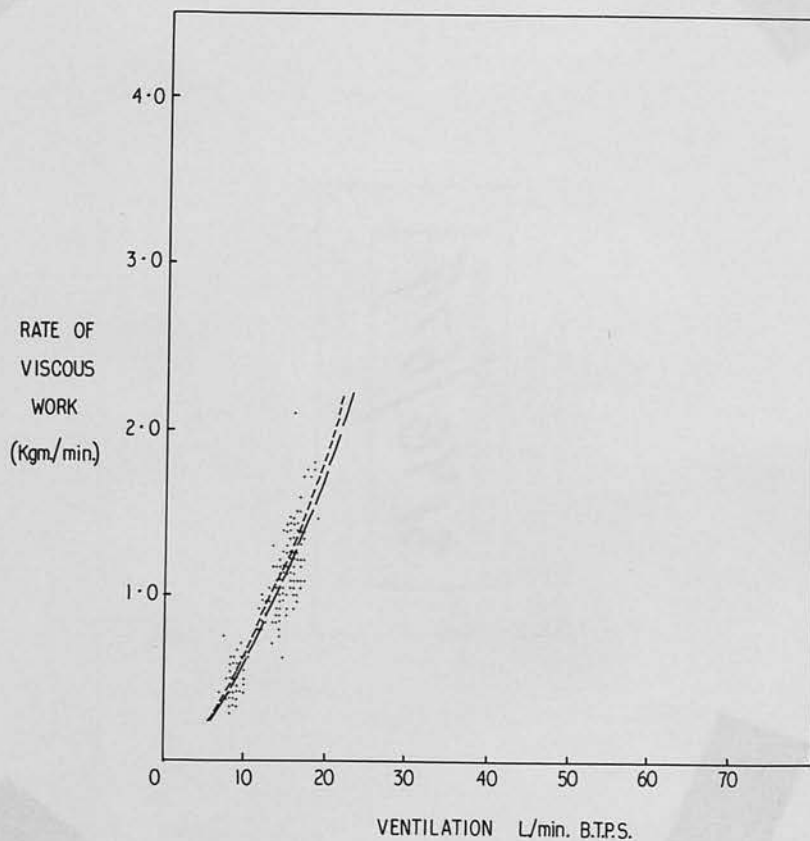


Figure 62

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 13.

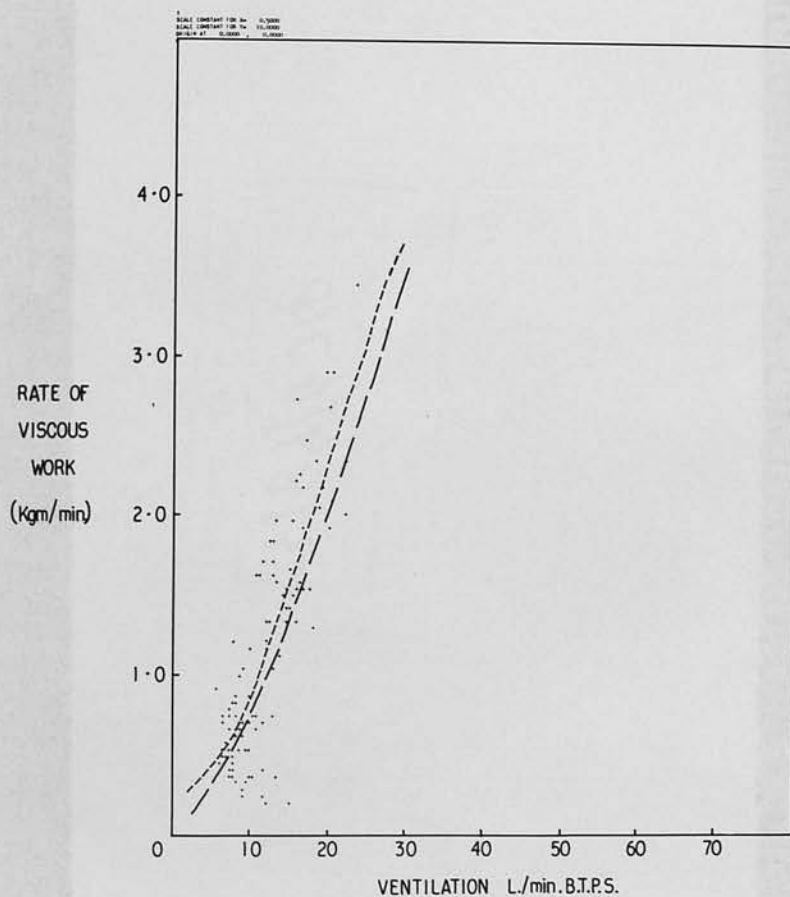


Figure 63

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 14.



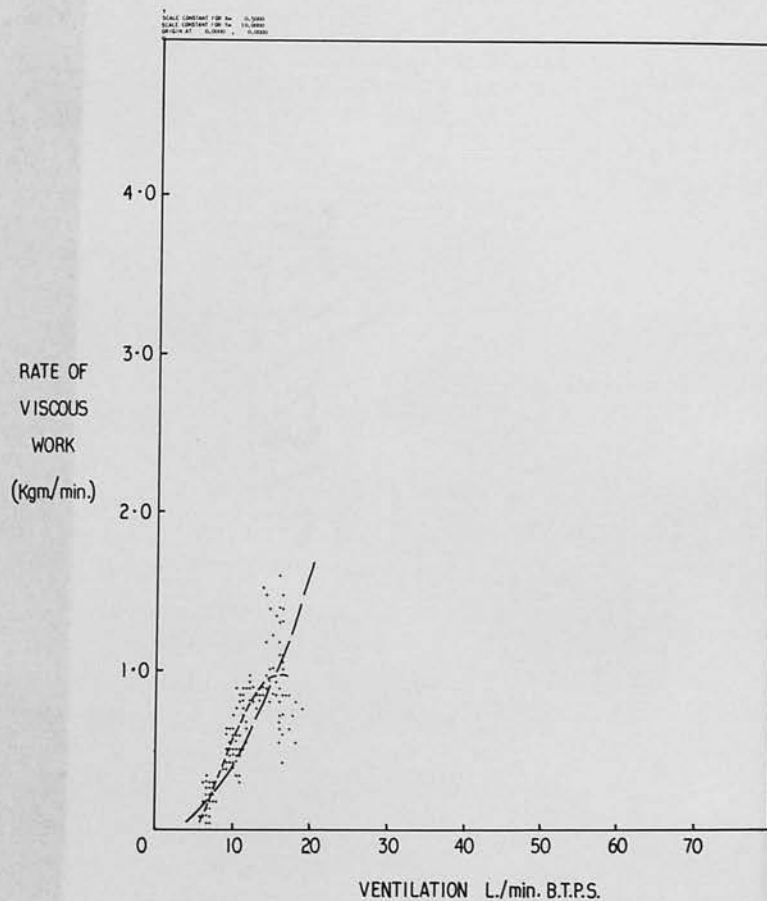


Figure 64

The relationships between the rate of viscous work on the lung (RVW) and the minute volume of ventilation ( $\dot{V}_E$ ). The short dotted line represents the cubic equation and the longer dashed line the logarithmic equation (see text). Data from Case 15.

#### 4. The Cubic Equation:

The equation:  $RVW = k_1 \dot{V}_E^2 + k_2 \dot{V}_E^3$  was, in fact, first proposed by

Rohrer (1925) in the form:

$$P = K_1 w_1 \eta \dot{V}_E + K_2 w_2 \rho \dot{V}_E^2 \quad (14)$$

where  $P$  = applied pressure differential due to viscous forces,

$K_1$  and  $K_2$  = constants

$w_1$  = constant dependent upon the length and diameter of the airway,

$\eta$  = viscosity of air

$w_2$  = constant dependent upon changes in diameter and directions  
of the airway

$\rho$  = density of the gas.

When expressed in the work form, of course, this equation (14) becomes:

$$P \cdot \dot{V}_E = \text{Work} = K_1 w_1 \eta \dot{V}_E^2 + K_2 w_2 \rho \dot{V}_E^3 \quad (15)$$

the form which we have been discussing. Rohrer (1925) therefore proposed

that these terms  $K_1 w_1$  regulated laminar flow and  $K_2 w_2$  regulated turbulent

flow. He calculated that from measurements on cadaver lungs, Reynolds

number ( $R$ ) where  $R = \frac{\rho v d}{\eta}$  (where density =  $\rho$ ,  $v$  = linear

velocity,  $d$  = diameter and  $\eta$  = viscosity) never exceeded the critical

value of 2,000 necessary for turbulent flow to occur. However, Rohrer

made an arithmetical error in his calculations, as Gaensler, Maloney

and Bjork (1952) have pointed out, and in fact turbulent flow does occur

in the airway, in all conditions except very quiet breathing. McIlroy,

Mead, Silverstone and Radford (1955) measured the lung tissue viscous

resistance by means of gases of equal kinematic viscosity, this being the ratio  $\frac{\eta}{\rho}$  or  $\frac{\text{viscosity}}{\text{density}}$ . By this means these authors were able to ensure that the character of the gas did not change the conditions for turbulent gas flow in the respiratory tract. As the pressure due to viscous forces depends upon the density of the gas mixture, they were able to measure the lung tissue viscous resistance by this means. Of more relevance to the present problem, however, are the results for values of  $K_1$  and  $K_2$  in Rohrer's equation that they obtained when helium and ethane were substituted for air. Helium would be expected, on the basis of its low density (16% of air) but similar viscosity (108% of air) to reduce  $K_2$  and increase  $K_1$ , but was found in fact to reduce  $K_1$ . With ethane (viscosity 151% of air, and density 117% of air) a reduction in  $K_1$  would be predicted, but in fact little effect was observed. In reviewing these results, Mead (1961) concluded that  $K_1$  and  $K_2$  should not be referred to as "laminar" and "turbulent" constants. He states that these results "serve to underline the inadequacy of present knowledge as to the aerodynamics of the respiratory passages".

If the equation (15) be divided throughout by  $\dot{V}_E^2$  it reduces to:

$$\frac{RVW}{\dot{V}_E^2} = K_1 w_1 + K_2 w_2 \rho \dot{V}_E \quad (16)$$

As  $w_1$  and  $w_2$  are constants, and transposing into the Otis form (equation 8), we can write:

$$\frac{RVW}{\dot{V}_E^2} = k_1 \frac{\Pi^2}{400} + k_2 \frac{2\Pi^2}{300} \dot{V}_E \quad (\text{where } k_1 \text{ and } k_2 \text{ are new constants})$$

or:

$$\frac{100RVW}{\dot{V}_E^2} = k_1 \frac{\Pi^2}{4} + k_2 \frac{2\Pi^2}{3} \dot{V}_E$$

But RVW has the dimensions of an area on the pressure volume diagram, and is  $P \cdot \dot{V}_E$  cm.H<sub>2</sub>O/litre/min., or  $\frac{P \cdot \dot{V}_E}{100}$  kg.m./min., where P is the pressure against viscous forces.

Therefore:

$$\frac{P \cdot \dot{V}_E}{\dot{V}_E^2} = \frac{\Pi^2}{4} k_1 + \frac{2\Pi^2}{3} k_2 \dot{V}_E$$

or:

$$\frac{P}{\dot{V}_E} = \frac{\Pi^2 k_1}{4} + \frac{2\Pi^2 k_2}{3} \dot{V}_E \quad (17)$$

Thus equation (17) becomes an expression for pulmonary viscous resistance, having the dimensions of pressure change/Flow rate. It is, in fact, this form of the equation and not that used to derive the relationship between minute volume ( $\dot{V}_E$ ) and inspiratory viscous work rate (RVW) that has been most studied. The usual form is that given by Mead and Whittenberger (1953).

$$\frac{P}{\dot{V}_E} = K_1 + K_2 \dot{V}_E, \text{ where } \dot{V}_E \text{ is expressed in litres/sec.}$$

It will therefore be apparent that the present values of  $k_1$  and  $k_2$  where  $\dot{V}_E$  is expressed in litres/min. are:

$$K_1 = \frac{\Pi^2 k_1}{4 \cdot 60} \quad \text{and} \quad K_2 = \frac{2\Pi^2 k_2}{3 \cdot 360}$$

In Table 41 values of these two components of the pulmonary resistance found in the literature are given, transposed into terms of  $k_1$  and  $k_2$  for comparison with the results in the present study.

The pulmonary resistance is made up to two parts, the airway



resistance and the lung tissue viscous resistance. The airway resistance is commonly measured by the body plethysmograph and simultaneous measurements of these two components have been made by Marshall and DuBois (1956) in normal man. The values of the coefficients  $k_1$  and  $k_2$  differ from those found by others in the present studies. Thus  $k_1$  for the normal subjects in the present studies is some 5 to 10 times the values of Mead and Whittenberger (1953) who were studied during rapid shallow breathing, and 2 to 3 times those of Magaria, Milic-Emili, Petit and Cavagna (1960) whose data refer to exercising subjects.

#### 5. The Negative Value of $k_2$ in the Present Experiments:

The negative value of  $k_2$  found in these experiments implies that the pulmonary viscous resistance during inspiration decreases as the minute volume increases. This is demonstrated by Figure 65 showing the plot of the equation:

$$\frac{RVW}{\dot{V}_E^2} 100 = \frac{k_1 \Pi^2}{4} + k_2 \frac{2\Pi^2}{3} \cdot \frac{1}{V_E} \quad (18)$$

for Case 7. How is this negative value to be explained? As shown in

Table 41, all previous workers have found a positive value for  $k_2$ .

However, it is most important to realise that all this previous work applies to measurements of total pulmonary resistance for both inspiration and expiration, whereas the present results, in Table 40, refer to the inspiratory resistance only.

It is known that the inspiratory pulmonary resistance, measured at one standard air flow of 0.5 litres/sec. or 30 litres/minute, is less

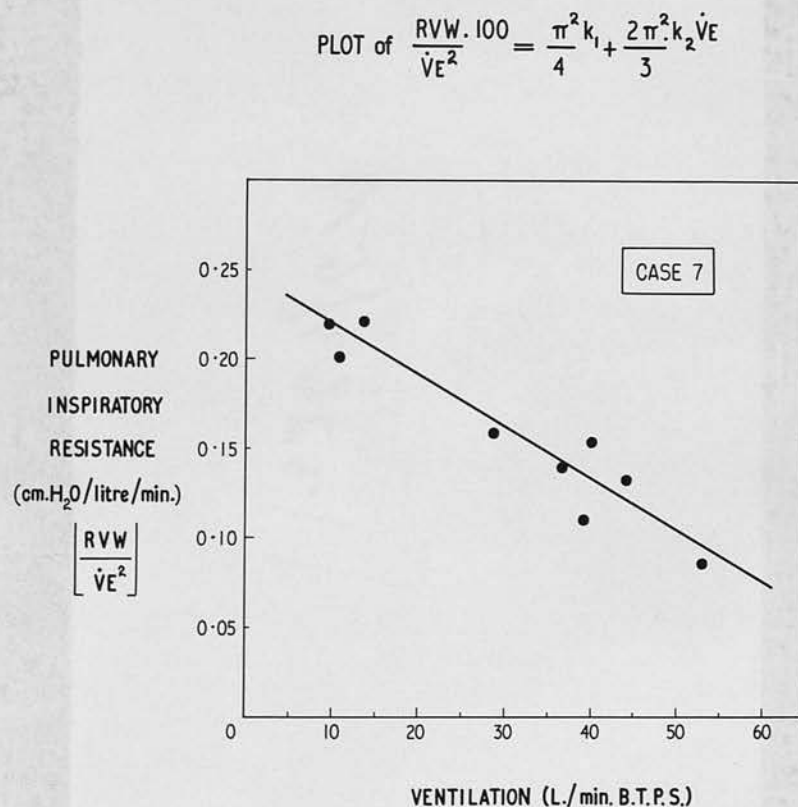


Figure 65

The relationship between the inspiratory pulmonary resistance ( $\frac{RVW}{\dot{V}_E^2}$ ) and the minute volume of ventilation ( $\dot{V}_E$ ). Data from Case 7. Line drawn by eye.

than the expiratory resistance at this airflow in both normal young subjects (Attinger, Monroe and Segal, 1956) in normal elderly subjects (Frank, Mead and Ferris, 1957), and in patients with emphysema (Attinger, Herschuler and Segal, 1956). In all these studies the inspiratory resistance is about 2/3rd the expiratory resistance. In addition it has long been known that the human bronchi dilate on inspiration, both from direct bronchoscopic examination (Chevalier Jackson, 1917) and from radiological observations (Bullowa and Gottlieb, 1920) in man. From the results of animal work, with both isolated lungs (Ellis, 1936) and in the anaesthetised dog (Nicholson and Trimby, 1940), this dilation of bronchi has been considered to be a purely passive reaction to lung inflation, as it is not abolished by lung denervation. If this result can be applied to man, it would follow that the bronchi dilate passively during inspiration. The amount of this dilatation would therefore be reasonably expected to increase as the tidal volume increases, although not necessarily in a linear fashion. It would therefore follow that the pulmonary inspiratory resistance would fall as the tidal volume rose. If the respiratory rate is relatively constant, this must mean that the inspiratory resistance would fall as the minute volume of ventilation increased. This, of course, is the result found in these experiments, as the negative values of  $k_2$  illustrate. This fall in inspiratory resistance as ventilation increases, as shown by the negative value of  $k_2$  is, moreover, compatible with the positive values of  $k_2$  shown by other workers, as summarised in Table 41. If the inspiratory resistance is less than the expiratory resistance, and if we postulate that

the expiratory resistance rises with increases in minute volume (Fry, Ebert, Stead and Brown, 1954) it follows that the overall pulmonary resistance, as measured in the results given in Table 41, will in fact increase as ventilation increases, as shown by the positive values of  $k_2$  given in that Table.

A further point is of some importance. The hyperventilation during which the present measurements were made was induced by carbon dioxide inhalation. The results in Table 41 were mainly obtained from experiments during which the subjects increased their ventilation voluntarily, thereby lowering their  $PCO_2$ . Is this difference in  $PCO_2$  levels likely to be of importance? The experimental evidence on the effects of carbon dioxide on the bronchial musculature is conflicting. There is evidence from work on isolated cats' lungs that carbon dioxide dilates bronchi which are tonically constricted (Nisell, 1950). However, in the intact, anaesthetised dog, Nadel and Widdicombe (1962) demonstrated an increase in pulmonary resistance on administration of carbon dioxide, which could be abolished by vagal section. By use of the body plethysmograph, to make measurements of airway resistance in man, Butler, Carno, Alcava and DuBois (1960) demonstrated that inhalation of up to 6% carbon dioxide had no effect on the airway resistance, and administration of 100% oxygen was also without effect. It would therefore appear probable that the carbon dioxide inhalation in these present experiments did not affect the airway component of the pulmonary inspiratory resistance. It is probably



important to note that the voluntary hyperventilation used so often in the studies quoted in Table 41, may, in fact, have resulted in an increase in pulmonary resistance. Thus Sterling (1967) has shown that hyperventilation sufficient to lower the end tidal  $\text{PCO}_2$  from 40 mm.Hg to 27 mm.Hg could increase the airway resistance in normal man from **4.30** cm. $\text{H}_2\text{O}$ /litre/sec, to **6.70** cm. $\text{H}_2\text{O}$ /litre/sec., this rise being abolished by the administration of atropine. This suggestion that hypocapnia can cause airway constriction is supported by the findings of Don and Robson (1965) in anaesthetised man. Their calculations of total flow resistance, from measurements of tracheal pressure during transient lung inflation at 1 litre/sec, showed that this flow resistance fell significantly when carbon dioxide was administered to the hypocapnic subject.

It would therefore seem likely that the addition of carbon dioxide as the stimulant to hyperventilation, as in these present experiments, may well prove to have considerably less effect on airway resistance than does the hypocapnia induced by voluntary hyperventilation, which was the method used by most previous workers.

#### 6. Absolute Values of Pulmonary Resistance:

The absolute values of pulmonary resistance are conventionally expressed at one standard flow rate, usually of 0.5 litres/sec, or 30 litres/min. By substitution in equation (18) of this value of 30 litres/min., and by use of the constants given in Table 40, it is possible to calculate the absolute values of pulmonary resistance on inspiration in these cases (Table 42). ~~In the normal subjects this ranged between 0.84 and 2.16~~

Inspiration occupies only a part of the respiratory cycle.

Thus a mean inspiratory flow of 30 litres/min. will, in fact, represent a greater mean rate of flow during the actual inspiratory period of each breath. If by substitution of  $\dot{V}_E = 30$  litres/min. in equation (18) one obtains an apparent value of inspiratory resistance in terms of cm.H<sub>2</sub>O/litre/min, this can be converted into the actual value of inspiratory resistance in cm.H<sub>2</sub>O/litre/sec., by multiplying this apparent value by  $\frac{60x}{100}$  where x is the percentage of the total respiratory cycle spent in inspiration for that patient. This value is obtained by counting the number of 1/5th second interruptions to the beam, in the experimental records of the respiratory loops, in the inspiratory and expiratory phases. When this is done the values in Table 42 are obtained.

In the normal subjects the values range from 3.0 to 6.2 cm.H<sub>2</sub>O/litre/sec with a mean of 4.3, compared to the mean value of 1.98 cm.H<sub>2</sub>O/litre/sec. (Attinger, Monroe and Segal, 1956) and  $2.0 \pm 0.7$  cm.H<sub>2</sub>O/litre/sec. (Frank, Mead, and Ferris, 1957) by direct measurements of transpulmonary pressure at a flow rate of 0.5 litres/second. In the bronchitic subjects the present values varied from 7.3 to 14.0, mean 9.6 cm.H<sub>2</sub>O/litre/sec., omitting negative values in cases 11 and 15. These arose, as inspection of Figures 60 and 64 shows, from the fact that the ventilation could not be increased above 20 litres/min. Attinger,

Herschufer and Segal (1956) found a mean value of 6.05 cm.H<sub>2</sub>O/litre/sec. in 12 emphysematous patients for the inspiratory pulmonary resistance. This present method, by use of equation (18) depends upon the assumption that the air flow is sinusoidal. As the duration of inspiration is not 50% of the total cycle (Table 42) this assumption only approximates to the truth.

cm.H<sub>2</sub>O/litre/sec. with a mean 1.37 cm.H<sub>2</sub>O/litre/sec. This compares with the mean values of 1.98 cm.H<sub>2</sub>O/litre/sec. obtained by Attinger, Monroe and Segal (1956) in eight young normal subjects for inspiratory pulmonary resistance. Frank, Mead and Ferris (1957) found a mean value of  $2.0 \pm 0.7$  cm.H<sub>2</sub>O/litre/sec. for inspiratory pulmonary resistance in 28 elderly subjects.

In the bronchitic patients the values of pulmonary inspiratory resistance varied from 1.68 to 6.00 cm.H<sub>2</sub>O/litre/sec., at the flow rate of 30/litres/min., with a mean value of 3.70 <sup>cm.H<sub>2</sub>O/</sup>litres/sec. In fact, the lowest value (1.68 cm.H<sub>2</sub>O/litre/sec.) was obtained in Case 12, where the regression coefficients  $k_1$  and  $k_2$  were not, in fact, significantly different from zero. These results compare with those of Attinger, Herschuer and Segal (1956) who found a mean value of 6.05 cm.H<sub>2</sub>O/litre/sec. in 12 emphysematous patients, again for the inspiratory pulmonary resistance.

These present results, therefore, show very similar values to these previous workers for the inspiratory pulmonary resistance, the value being, of course, much increased in the bronchitic subjects.

#### 7. An Alternative Form of Relationship between RVW and $\dot{V}_E$ :

In 1952, Ainsworth and Eveleigh demonstrated that an equation of the form:  $P = RQ^n$  (19) represented their results relating alveolar pressure and airflow data, adequately for seven normal subjects, when the rate of flow (Q) exceeded